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P R O C E E D I N G S

COURT SECURITY OFFICER: All rise.

(Jury in.)

THE COURT: All right. Please be seated.

Good morning, Ladies and Gentlemen.

Thank you for being here timely.

Good morning, Counsel.

Ready to proceed?

MR. LEE: We're ready to proceed, Your
Honor.

THE COURT: Who will be your next

1 witness?

2 MR. LEE: Your Honor, the first witness
3 will be by videotaped deposition, and I will make an
4 introduction, if that's okay.

5 THE COURT: Absolutely.

6 MR. LEE: Good morning, Ladies and
7 Gentlemen of the Jury.

8 The first witness you will hear from
9 today is Pablo Casali, who you've heard mentioned during
10 the evidence.

11 Dr. Casali has a medical degree with a
12 specialty in immunology. He worked at the Scripps
13 Clinic and Research Foundation, the National Institute
14 of Health, and New York University.

15 While at New York University, Dr. Casali
16 collaborated with BASF, that you now know later became
17 part of Abbott.

18 Your Honor, of the running time, 11
19 minutes and 1 second are allocated to Abbott; 3 minutes
20 and 56 seconds to Centocor.

21 (Video playing.)

22 QUESTION: With respect to your work with
23 human antibodies, can you describe generally that work
24 at Scripps, NIH, and then at NYU?

25 ANSWER: I would say that work at -- very

1 hard work on human antibodies really came into being at
2 NIH -- at NIH in the mid-'80s and late '80s.

3 My laboratory was at the cutting edge
4 while the -- the leading laboratory in the construction
5 of human antibodies. We were the first ones to generate
6 monoclonal -- human monoclonal antibody of predator,
7 mean specificity, and isotype.

8 And we generated antibodies high specific
9 for viruses, human pathogen viruses as well as
10 self-component -- component of the body, such as
11 thyroglobulin, a hormone of the thyroid, insulin, DNA,
12 et cetera.

13 And that work continued at NYU. It was
14 expanded, and eventually provided significant insights
15 into the -- into the mechanisms of generation of human
16 autoantibodies in health disease.

17 QUESTION: Can you describe for us
18 briefly what hybridoma technology is with respect to
19 mouse antibodies?

20 ANSWER: With respect to --

21 QUESTION: Mouse.

22 ANSWER: Mouse monoclonal antibodies?

23 QUESTION: Yes.

24 ANSWER: Cell lines. Essentially, it
25 consists in taking a fraction, a pool of B-cells or

1 B-lymphocytes. Those are the cells that make
2 antibodies, or can make antibodies. Possibly enriched
3 for a certain specificity; that is, possibly enriched
4 for clones that are capable of producing the antibody
5 that one wants to eventually select for, and fuse them
6 with a fusion partner, a preconstructed fusion partner,
7 in general, a non-secretor, that is, a fusion partner
8 that will not provide any additional different antibody
9 specificity to the resulting hybrid.

10 Fuse it to a fusion partner, and then
11 select the resulting hybrid for secretion of the
12 antibody of the desired specificity.

13 QUESTION: What is the purpose of fusing
14 the two cells?

15 ANSWER: The main purpose of fusing the
16 two cells, the one of stabilizing the cell hybrid, the
17 producer of antibody.

18 QUESTION: Is this sometimes referred to
19 as immortalizing the cell?

20 ANSWER: Yes.

21 QUESTION: So the B-cell is producing the
22 antibody, and the fusion cell is stabilizing the
23 resulting hybridoma?

24 ANSWER: Yes.

25 QUESTION: Are there any particular

1 problems in making human hybridomas compared to mouse
2 hybridomas? And let's focus on the early 1990s, if we
3 could.

4 ANSWER: Yes, there -- there were and
5 still are big problems in that in a mouse, one can
6 enrich the mouse for B-cells with a desired specificity
7 simply by immunizing the mouse, injecting the mouse with
8 whatever one wants to generate.

9 For instance, if I want to generate an
10 antibody to influenza virus, I can inject the mouse with
11 influenza virus. And then take the spleen cells from
12 the mouse, and those spleen cells will be highly
13 enriched in precursors to influenza. And, therefore,
14 when I fuse the spleen cells with the fusion partner,
15 the probability of eventually coming down with hybrids
16 making good anti-influenza antibodies would be very
17 high.

18 Obviously, one cannot, because of ethical
19 reasons, inject humans, unless one deals with certain
20 vaccines. But obviously, when one wants to generate an
21 antibody to a self-component, such as insulin, or any
22 other hormone of the body, one cannot inject a human
23 with anything.

24 So one has to rely on the natural
25 occurrence of B-cells in the body of that individual,

1 the donor, for that particular antigen.

2 And what we first realized was that,
3 while in certain cases it is possible to choose donors
4 that would have a high frequency of antibody-producing
5 cells to a certain self-component, such as, for example,
6 taking B-cells from a patient with Lupus for -- in order
7 to produce monoclonal antibodies to DNA, because
8 anti-DNA monoclonal antibodies are a trait of Lupus, a
9 characteristic trait of Lupus.

10 In other cases, that is not possible
11 simply because the frequency of B-cells making an
12 antibody to a particular antigen, a self-antigen, is
13 very low. So the game become very difficult, becomes a
14 very low-probability game.

15 QUESTION: And so I'm focusing you really
16 on the 1990s and your work. And my question is whether
17 there were any particular problems with immortalizing a
18 human B-cell, if you had the -- with the right B-cell.

19 ANSWER: The answer is no, because at
20 that time, we pioneered the enrichment of B-cells by
21 transformation with Epstein-Barr virus. So instead of
22 using primary B-cells, we would use EBV-transformed
23 B-cells. And EBV-transformed B-cells are proliferating
24 nicely in vivo -- in vitro -- I'm sorry -- as opposed to
25 primary B-cells, which will die within two or three

1 days.

2 So then we would use those B-cells to
3 fuse -- as fusion to fuse with the fusion partner, or
4 the hybridoma fusion partner. And, again, the answer is
5 no, provided that one used EBV-transformed B-cells, as
6 we did, and provided that one used, as we did, as a
7 fusion partner, a cell line which was already, per se,
8 the result of a fusion of a mouse non-secretor myeloma
9 with a human B-cell that was selected for producing no
10 antibodies.

11 QUESTION: Now, in 1991, were you
12 contacted by BAS Research (sic) to engage in a
13 collaboration with them?

14 ANSWER: BASF, yes.

15 QUESTION: Yes. And do you understand
16 BASF to have later been acquired by Abbott Laboratories?

17 ANSWER: Yes.

18 QUESTION: Who contacted you from BASF?

19 ANSWER: The CEO, Bob Kamen.

20 QUESTION: And did you then enter into a
21 collaboration with BASF?

22 ANSWER: Yes.

23 QUESTION: With whom did you work?

24 ANSWER: With Bob Kamen himself and
25 Jochen -- Jochen Salfeld or --

1 QUESTION: Salfeld.

2 ANSWER: Salfeld, Salfeld, Jochen

3 Salfeld.

4 And then there was another German guy who
5 was back in Germany, left -- went back to Germany three,
6 four years later, whose name I cannot remember.

7 QUESTION: If I suggested to you Achim
8 Moller, would that refresh your recollection?

9 ANSWER: Achim Moller, yes.

10 QUESTION: How long did the collaboration
11 last?

12 ANSWER: The collaboration, I think, was
13 originally for two years. Might have been extended to
14 three years, but I don't have a precise recollection
15 of -- of the extension.

16 QUESTION: And during the collaboration,
17 one other person in your lab worked on the project
18 approximately full-time?

19 ANSWER: Yeah. As I mentioned, there was
20 a person at -- to begin with who worked full-time on the
21 project.

22 QUESTION: What was the purpose of the
23 collaboration?

24 ANSWER: The purpose of the collaboration
25 was the one of generating human monoclonal antibody to

1 TNF-alpha, tumor necrosis factor-alpha.

2 QUESTION: And what do you mean by human
3 monoclonal antibody?

4 ANSWER: I mean a human monoclonal
5 antibody that will bind TNF-alpha with high strength,
6 and, therefore, will be specific for TNF-alpha, and
7 could possibly be used in the clinic to neutralize
8 TNF-alpha.

9 QUESTION: What do you mean by
10 neutralize?

11 ANSWER: I mean by neutralizing, binding
12 TNF-alpha, and thereby neutralizing the biological
13 activity of TNF-alpha.

14 QUESTION: Do some antibodies bind to a
15 protein but not neutralize the protein?

16 ANSWER: Yes.

17 QUESTION: So your goal was to have an
18 antibody that both bound to the protein and neutralized
19 it?

20 ANSWER: Yes.

21 QUESTION: What technology did the
22 collaboration intend to use to generate such an
23 antibody?

24 ANSWER: The collaboration, as far as
25 my -- my side, meaning my lab, was concerned was the one

1 of -- was to use my technology, which, again, had been
2 successful in the generation of many human monoclonal
3 antibodies for different self-components.

4 QUESTION: And you obtained the blood
5 samples of these patient populations with the
6 expectation that they would have anti-TNF antibodies?

7 ANSWER: Yes.

8 QUESTION: From where did you obtain the
9 blood samples?

10 ANSWER: If I remember correctly, they
11 were virtually all from NYU. Perhaps a few samples from
12 the rheumatoid arthritis patients were from -- in
13 addition to NYU, were also from the NIH.

14 QUESTION: And did these blood samples,
15 in fact, have TNF-alpha antibodies?

16 ANSWER: Well, certainly not in the level
17 that we expected them to have.

18 QUESTION: And is that -- when you say
19 that, do you mean the concentration of antibodies or
20 their characteristics as neutralizing or not
21 neutralizing?

22 ANSWER: Both.

23 QUESTION: So the blood samples both did
24 not have a substantial amount of antibody in them, and
25 the antibody was non-neutralizing?

1 ANSWER: Yes.

2 QUESTION: Did that surprise you?

3 ANSWER: Yes.

4 QUESTION: I want to take you back to the
5 early 1990s --

6 ANSWER: Yes.

7 QUESTION: Again, your understanding of
8 why it was that, to your surprise, the antibodies from
9 the patient samples were non-neutralizing.

10 ANSWER: Let me, perhaps, answer in a
11 different way that your question would formally require.

12 QUESTION: Okay. Thank you.

13 ANSWER: I expected those samples, the
14 blood samples, to include B-cells that would easily
15 produce, quote, good antibodies.

16 And what I mean for that is, IgG's,
17 binding TNF-alpha with a decent affinity. But I didn't.
18 So what I found were IgM, with a low affinity. And
19 those were not different from the ones I could find in
20 healthy subjects. This is what I meant when I say no
21 different from healthy subjects.

22 QUESTION: Was your collaboration with
23 BASF, therefore, not successful in producing a
24 neutralizing human antibody against TNF-alpha?

25 ANSWER: It was not.

1 QUESTION: To this day, are you aware of
2 anyone who has generated a human antibody against
3 TNF-alpha using hybridoma technology, a neutralizing
4 human antibody?

5 ANSWER: A modify, meaning -- no, I'm
6 not.

7 QUESTION: When you were working during
8 the collaboration with BASF, how many antibodies did you
9 generate to TNF-alpha?

10 ANSWER: Many.

11 QUESTION: How many?

12 ANSWER: Many. I -- I don't recall how
13 many.

14 QUESTION: More than a hundred?

15 ANSWER: Perhaps close to a hundred.

16 QUESTION: Did you generate any
17 antibodies that bound with high affinity to TNF-alpha?

18 ANSWER: No.

19 QUESTION: None?

20 ANSWER: No.

21 (End of video clip.)

22 THE COURT: All right. Mr. Lee, who will
23 be your next witness?

24 MR. LEE: The next witness, Your Honor,
25 will be one more video clip. This is Dr. Le, who is one

1 of the inventors of the '775 patent. Dr. Junming Le is
2 his name. You've seen him on the cover of the patent
3 itself.

4 Dr. Le worked at New York University and
5 was supported by Centocor. Mr. Le is one of the
6 inventors of the '775 patent, and you will see
7 approximately 15 minutes of his testimony.

8 Your Honor, the allocation is 13 minutes
9 and 17 seconds to Abbott; 2 minutes and 16 seconds for
10 Centocor.

11 (Video playing.)

12 QUESTION: If you could, look at the
13 front of your patent at the inventors. Could you
14 describe your understanding of what each of them
15 contributed to the invention?

16 ANSWER: I -- I don't really know what
17 they do.

18 QUESTION: What was your contribution to
19 the invention?

20 ANSWER: My contribution to this project
21 is that I made the antibody A2, from A to Z.

22 QUESTION: Did your work in making A2
23 begin on or around December 22nd, 1988?

24 ANSWER: On December, yes, 22nd. That's
25 the right date.

1 QUESTION: So on May 15, 1989, you
2 identified the hybridoma that produced A2; is that
3 correct?

4 ANSWER: Right.

5 QUESTION: If you could turn to Page 43
6 of your notebook, the entry marked August 2nd to
7 August 9, 1989, and can you read into the record your
8 handwriting there?

9 ANSWER: Neutralization of TNF by human
10 mAB 7.T.1.

11 QUESTION: This is an experiment you
12 performed on a human antibody to TNF; is that correct?

13 ANSWER: This is the neutralization test,
14 but we just tried to test that this particular antibody
15 is claimed to be a human IgM monoclonal antibody for
16 TNF.

17 This antibody was from Dr. Uli Hammenlin
18 at Sloan-Kettering Institute.

19 QUESTION: Did you know Dr. Hammenlin --

20 ANSWER: Yes.

21 QUESTION: -- from your time at
22 Sloan-Kettering?

23 ANSWER: Yes.

24 QUESTION: Were you aware -- familiar
25 with this antibody before you received it?

1 ANSWER: No, I wasn't familiar.

2 QUESTION: What -- what sort of work was
3 Dr. Hammenlin doing at this time?

4 ANSWER: Hammenlin was an immunologist.
5 He did a lot of stuff in -- stuff in different fields of
6 immunology.

7 And for this particular experiment, I
8 believe that Centocor, before deciding which antibody
9 they want to go commercially, they want to compare A2
10 with all other antibody available. So this is one of
11 them.

12 They -- they received this antibody from
13 Uli Hammenlin, and they want me to test whether it shows
14 any potent neutralization activity.

15 QUESTION: And you understood that
16 Centocor was considering whether to go forward with the
17 A2 antibody --

18 ANSWER: Or with something else, yes.

19 QUESTION: -- and one of the
20 possibilities for something else was --

21 ANSWER: They only can pick one, the very
22 best one.

23 QUESTION: Okay. And 7.2.1 was one of
24 the antibodies they were considering?

25 ANSWER: Yes.

1 QUESTION: And 7.2.1 was a fully human
2 antibody, correct?

3 ANSWER: I -- I'm not aware of the --
4 the -- the nature of this antibody, but according to
5 Centocor, yes, this is a human IgM antibody.

6 QUESTION: Right. And you would have
7 understood that to have been made using human
8 hybridomas?

9 ANSWER: That I don't know.

10 QUESTION: When you wrote the words human
11 monoclonal antibody, what would your understanding have
12 been about what that is?

13 ANSWER: I just copy what the Centocor
14 people told me.

15 QUESTION: Okay. And in 1989, what would
16 your understanding have been about how a human antibody
17 was made?

18 ANSWER: I understood at the time that
19 there were not so many successful human antibody
20 available. There's a lot of people fail in making true
21 human antibodies.

22 QUESTION: What were the difficulties in
23 making a true human antibody?

24 ANSWER: I believe that the most
25 important part is, there's no very effective fusion

1 partner, like the SP2 or zero cells for the murine.

2 QUESTION: So it was difficult to make a
3 human hybridoma?

4 ANSWER: Without proper fusion partners.

5 QUESTION: And you were aware of many
6 failures in the field of making human hybridomas?

7 ANSWER: Yes.

8 QUESTION: And you yourself did not
9 attempt to make a human hybridoma?

10 ANSWER: No.

11 QUESTION: Why not?

12 ANSWER: I didn't have the partner.

13 QUESTION: You did not have a suitable
14 fusion partner to make a human hybridoma?

15 ANSWER: Right.

16 QUESTION: Are you aware of, in the
17 course of your project for Centocor, testing any human
18 antibodies other than 7.T.1?

19 ANSWER: Yes. I tested some more
20 antibodies, but this probably is the only human
21 antibody.

22 QUESTION: Okay.

23 ANSWER: The others are all murine
24 antibodies.

25 QUESTION: This is the only

1 human antibody --

2 ANSWER: I test for Centocor.

3 QUESTION: We're going to drive the court
4 reporter crazy.

5 ANSWER: Sorry.

6 QUESTION: And the only human TNF
7 antibody you tested did not work, correct?

8 ANSWER: No.

9 QUESTION: It didn't neutralize, correct?

10 ANSWER: No.

11 QUESTION: That's the 7.T.1 antibody?

12 ANSWER: Yes.

13 QUESTION: Were there problems with
14 murine antibody as a human therapy?

15 ANSWER: Was there any problem?

16 QUESTION: Is there a problem with use of
17 a murine antibody as a human therapy?

18 ANSWER: One of the problems could be the
19 antigenicity, because the human body can recognize a
20 murine antibody as a foreign protein. So, therefore,
21 they can produce antibody that will bind -- I mean,
22 diminish the effect -- effectiveness of this murine
23 antibody when you inject it into the human body.

24 QUESTION: I'd like to also show you what
25 has previously been marked as Defendants' Exhibit 110.

1 If you could identify this document for the record.

2 ANSWER: Yes.

3 QUESTION: Can you identify this document
4 for the record, please?

5 ANSWER: Well, I can't -- the document
6 is -- it's a letter, but there's a figure that's the
7 results of my experiment. That also you can find in my
8 notebook, I guess.

9 QUESTION: And that's the experiment --

10 ANSWER: Yeah.

11 QUESTION: -- shown on Page 45?

12 ANSWER: 45, yes.

13 QUESTION: And this is the experiment
14 that showed that the human antibody, 7.T.1, had no
15 neutralizing activity?

16 ANSWER: Doesn't work.

17 QUESTION: Doesn't work?

18 ANSWER: Yes.

19 QUESTION: And this is the only human
20 antibody you tested?

21 ANSWER: I tested, yes.

22 QUESTION: What involvement did you have
23 in the patent process?

24 ANSWER: There is an industrial liaison
25 at NYU Medical Center. They handle all the patent

1 issues. They have connection with the law firms. And
2 what we did mainly is provide the raw data.

3 QUESTION: Okay. I'd like to show you
4 what's previously been marked as Defendants' Exhibit 96.
5 And if you could read that over.

6 ANSWER: What's the question?

7 QUESTION: Does this refresh your
8 recollection that you contributed some portion of the
9 writing of the first application?

10 ANSWER: No, I didn't do it.

11 QUESTION: And you never had possession
12 of a fully human antibody to TNF; that's correct?

13 That's correct?

14 ANSWER: It's correct.

15 QUESTION: And you're not aware of anyone
16 at Centocor that had possession of a fully human
17 antibody to TNF?

18 ANSWER: I was not aware.

19 QUESTION: My question is, do you
20 recognize the application that begins at Bates
21 No. 1361958 as the original application that you filed
22 and that you provided an oath, stating that you've read
23 it?

24 ANSWER: Yeah. This again, it's like 18
25 years ago. I really cannot tell you.

1 QUESTION: Uh-huh.

2 ANSWER: I suppose so, yeah.

3 QUESTION: Okay. If you could turn to
4 Page 8 of the document.

5 ANSWER: What's that?

6 QUESTION: Page 8 of the document, which
7 is Bates No. 1361966.

8 And I'd ask you if you could read to
9 yourself the material that begins under monoclonal and
10 chimeric antibodies. If you could read that to the
11 summary of the invention, which is two pages away. And
12 I'll have some questions for you.

13 ANSWER: Okay. What was your question?

14 QUESTION: Turning to Page 8, this is
15 from your first application, correct?

16 ANSWER: Page 8? This one?

17 QUESTION: Do you have Page 8 in front of
18 you?

19 ANSWER: Yes.

20 QUESTION: There is a reference to a
21 problem with murine antibodies. Do you see that?

22 ANSWER: Yes, as I told you earlier.

23 QUESTION: And this is the problem that
24 murine antibodies can themselves cause an immune
25 reaction, correct?

1 ANSWER: Right.

2 QUESTION: Okay. And then if you turn to
3 Page 9 of your application, the application notes that
4 human monoclonal antibodies could solve the problem of
5 murine antibodies, at least theoretically, correct?

6 ANSWER: It would be better.

7 QUESTION: But in your application, you
8 note that there were problems with making human
9 antibodies, correct?

10 ANSWER: Yeah, because in previous
11 literature, the document is that you tried to use EBV to
12 immobilize the human B-cells with very little success.

13 QUESTION: And this is what you were
14 saying before, that there isn't a suitable fusion --

15 ANSWER: Partner, yes.

16 QUESTION: -- partner to make the human
17 hybridomas?

18 ANSWER: Yes.

19 QUESTION: And that was a problem that
20 the art had not solved as of 1991, correct?

21 ANSWER: I -- I'm not aware of them.
22 Maybe somebody already solved in the lab that they've
23 never published.

24 QUESTION: Certainly not a problem that
25 you solved, correct?

1 ANSWER: Correct.

2 QUESTION: And the chimeric antibody
3 invention was to solve the problem of murine antibodies
4 and the immune response that they would cause, correct?

5 ANSWER: Yes.

6 QUESTION: And it was to solve the
7 problem of human antibodies, which is that they couldn't
8 be made and they didn't work, correct?

9 ANSWER: That I don't know.

10 QUESTION: In fact, you hadn't made them
11 and you didn't --

12 ANSWER: I didn't make them, yeah.

13 QUESTION: That's correct?

14 ANSWER: Yeah.

15 (End of video clip.)

16 THE COURT: All right. Who will be next,
17 Mr. Lee?

18 MR. LEE: Your Honor, the exhibits that
19 were referred to, Exhibits 96 and 110, were preadmitted.

20 We would call at this time Dr. James
21 Marks.

22 COURTROOM DEPUTY: Raise your right hand,
23 please.

24 (Witness sworn.)

25 MR. LEE: May I proceed, Your Honor?

1 THE COURT: Sure. Please do.

2 JAMES MARKS, M.D., DEFENDANTS' WITNESS, SWORN

3 DIRECT EXAMINATION

4 BY MR. LEE:

5 Q. Good morning, Dr. Marks.

6 A. Good morning, Mr. Lee.

7 Q. Would you introduce yourself to the ladies and
8 gentlemen of the jury.

9 A. Yes. My name is James Marks.

10 Q. Would you tell us a little bit about yourself
11 personally?

12 A. Yes. I was born and raised in Southern
13 California, where I grew up. I went to school largely
14 in Northern California, where I ended up settling and
15 currently live. I'm married, and I have a daughter
16 who's 21 years old and has a year of college to go.

17 Q. Where do you work, Dr. Marks?

18 A. I am a professor of anesthesia at the
19 University of California, San Francisco, and I work at
20 San Francisco General Hospital.

21 Q. Do you have a position at San Francisco
22 General Hospital?

23 A. Yes. I am Chief of Anesthesia at San
24 Francisco General Hospital.

25 Q. And would you tell the jury a little bit about

1 what you do as a member of the faculty at the hospital?

2 A. Yes. So I am what's called a physician
3 scientist. So that means I am a medical doctor and a
4 practicing physician who sees patients. And I'm also a
5 scientist who has a large research laboratory.

6 San Francisco General Hospital is a large
7 teaching hospital affiliated with the University of
8 California-San Francisco. It's also a county hospital
9 in what is called a safety net hospital, which means we
10 largely take care of patients who cannot get care
11 anywhere else because they either have no health
12 insurance or they have health insurance that other
13 hospitals in the city will not accept.

14 At San Francisco General Hospital, I am Chief
15 of the Department of Anesthesia, which means I supervise
16 a group of around 150 people, who include practicing
17 anesthesiologists, nurse anesthetists, as well as about
18 60 scientists doing research in anesthesia-related
19 fields.

20 One day a week, I actually practice anesthesia
21 in the Emergency Department and operating rooms of San
22 Francisco General Hospital.

23 In the rest of my time, I run a research
24 laboratory that consists of around 15 scientists. And
25 what we basically do is invent technologies for making

1 better antibody drugs. And then we are making
2 antibodies for the treatment of specific human diseases,
3 largely cancer and infectious diseases.

4 Q. Dr. Marks, in addition to your research and
5 your medical duties, do you have an association with any
6 biotechnology companies?

7 A. Yes. I'm a co-founder of a biotechnology
8 company called HERMES Biosciences, and HERMES
9 Biosciences is developing new types of cancer drugs that
10 are currently in clinical trials for a number of
11 different cancers.

12 I'm on the Scientific Advisory Board of a
13 major pharmaceutical company where I advise them on ways
14 to make and develop antibodies. And I'm on the
15 Scientific Advisory Board of two other biotechnology
16 companies.

17 Q. And could you give us a little bit more
18 information about your educational background?

19 A. Yes. I was an undergraduate student at the
20 University of California-Berkeley where I majored in
21 biochemistry. I then went straight to medical school at
22 the University of California-San Francisco, receiving an
23 M.D. degree in 1979.

24 I then completed residency in internal
25 medicine and anesthesia and did a fellowship in

1 intensive care medicine. I'm board-certified in all
2 three specialties.

3 After two years on the faculty at the
4 University of California, I then went to Cambridge,
5 England, where I studied in the laboratory of
6 Dr. Gregory Winter, and received a Ph.D. in molecular
7 biology.

8 Q. What year did you receive your Ph.D. in
9 molecular biology?

10 A. 1992.

11 Q. Now, we've heard mention of Dr. Winter
12 previously. Who was or is Dr. Gregory Winter?

13 A. Dr. Winter is considered the father of modern
14 antibody engineering. He has invented the two most
15 important technologies that are currently used to make
16 therapeutic antibodies.

17 Q. And what years did you study under Dr. Winter?

18 A. Between 1988 or '89 and 1992.

19 Q. Now, during -- what experience, if any, do you
20 have in the field of antibody engineering?

21 A. I have worked continuously in the field of
22 antibody engineering since 1989.

23 Q. So for approximately 21 years?

24 A. That is correct.

25 Q. Now, I'm going to ask you the question I've

1 asked each of the Centocor witnesses.

2 Have you yourself ever isolated a fully human
3 TNF-alpha antibody?

4 A. Yes, I have.

5 Q. Now, you've sat here during the course of the
6 trial, correct?

7 A. Yes, I did.

8 Q. And you've heard me ask that question of every
9 witness Centocor called, correct?

10 A. Yes, I did.

11 Q. And none of them had ever isolated a TNF-alpha
12 antibody themselves, correct?

13 A. That's correct.

14 Q. But you did?

15 A. Yes, I did.

16 Q. When did you do it?

17 A. In approximately 1991.

18 Q. Was that a fully human -- I'm sorry. Was that
19 fully -- was it a fully human TNF-alpha antibody?

20 A. Yes, it was.

21 Q. Did it work?

22 A. What do you mean by work?

23 Q. Did it have a high affinity?

24 A. No, it did not.

25 Q. When you isolated the human anti-TNF-alpha

1 antibody, was it easy?

2 A. No. It was very, very difficult. It was a
3 culmination of approximately three years of work by a
4 team of scientists developing a completely new way to
5 make human antibodies. And we tested that new way on a
6 variety of different antigens, and one of them was TNF.

7 Q. And the antibody that you generated that was
8 for TNF was not high affinity, correct?

9 A. No. No, it was not. It was typical of the
10 type of antibodies that we could obtain from those --
11 the early stages of that technology, low affinity.

12 Q. Now, you were here when we heard the videotape
13 deposition of Dr. Casali and Dr. Le?

14 A. Yes, I was.

15 Q. And each of them actually generated
16 anti-TNF-alpha antibodies, correct?

17 A. That's correct.

18 Q. Now, I'm going to come back to your own
19 antibody a little bit later, but let me go back to your
20 background.

21 Have you authored any publications?

22 A. Yes, I have.

23 Q. Approximately how many?

24 A. About 160.

25 Q. And what is the field or what is the general

1 field of your publicly sayings?

2 A. Virtually all of them are related to different
3 aspects of antibody engineering.

4 Q. And during the cross-examination of
5 Dr. Ghrayeb, were you here for that?

6 A. Yes, I was.

7 Q. He mentioned a publication by a Dr. Marks. Do
8 you remember that?

9 A. Yes.

10 Q. Is that one of your publications?

11 A. Yes, it is.

12 Q. Are you also the named inventor on any United
13 States patents?

14 A. Yes, I am.

15 Q. Approximately how many?

16 A. Approximately 23 United States patents.

17 Q. All right. Now, have you been retained to
18 serve as an expert in this case?

19 A. Yes, I have.

20 Q. By whom?

21 A. By Abbott.

22 Q. How are you being compensated?

23 A. I am being paid an hourly rate for my time.

24 Q. Now, the jury has heard lots of evidence about
25 Humira. You're familiar with Humira, correct?

1 A. Yes. Yes, I am.

2 Q. Were you involved yourself in developing any
3 of the technologies that helped bring Humira to the
4 marketplace?

5 A. Yes, I was. I am an inventor of antibody
6 phage display, which I believe the jury has already
7 heard was used as one of the technologies to make
8 Humira.

9 Q. All right. You were here yesterday when
10 Dr. Salfeld testified?

11 A. Yes, I was.

12 Q. And he described briefly phage display and
13 analogized it to needles in haystacks in a field.

14 A. That was a good analogy.

15 Q. And are there patents on phage display?

16 A. There are many.

17 Q. Are you a named inventor on those patents?

18 A. On at least ten of them.

19 Q. And have companies, who are trying for the
20 last 20 years -- are there companies who are trying to
21 produce antibodies that have taken licenses under your
22 patents?

23 A. Yes, there are.

24 Q. Approximately how many?

25 A. At least a half a dozen.

1 Q. Okay. And has any of those companies been
2 successful in using phage display to produce a
3 therapeutic product for the marketplace?

4 A. Only Abbott.

5 Q. Only Abbott of all of them?

6 A. That's correct.

7 To the present time, Abbott has made the only
8 drug with phage display that has been licensed by the
9 Food & Drug Administration.

10 Q. And as a result of their taking a license from
11 you and your colleagues, have you received compensation
12 through Abbott for the use of your inventions?

13 A. Yes, I have.

14 Q. Approximately how much?

15 A. Approximately \$2.7 million.

16 Q. And that's for your invention of phage
17 display, correct?

18 A. That's correct.

19 Q. Now, do you currently receive any compensation
20 at all that's related to Humira?

21 A. Yes, I do.

22 Q. How much?

23 A. Approximately \$20,000 a year for the next two
24 to three years.

25 Q. And is that dependent upon how much Humira is

1 sold?

2 A. No, it is not.

3 Q. Have you ever been an employee of Abbott?

4 A. No, I have not.

5 Q. Other than participating in the invention of
6 phage display, did you participate in the invention of
7 Humira in any way?

8 A. No, I did not.

9 Q. Will the compensation you receive as an expert
10 witness be effect -- I'm sorry -- will your compensation
11 as an expert witness be affected in any way by the
12 outcome of this case?

13 A. No, it will not.

14 Q. Do you have any financial interest in the
15 outcome of the case?

16 A. No, I do not.

17 Q. And have the opinions that you've formed
18 concerning the issues the jury has to decide been
19 influenced in any way by the amounts that Abbott paid
20 you for licensing your patents?

21 A. No, they have not.

22 MR. LEE: Your Honor, we would offer
23 Dr. Marks as an expert in the field of antibody
24 technologies, subject to objections from the other side.

25 THE COURT: Well, the Court will permit

1 him to express opinions as was previously disclosed in
2 his expert report.

3 MR. LEE: Yes, Your Honor.

4 Q. (By Mr. Lee) Now, let's go to a little bit of
5 background. The jury has heard some of this before, so
6 we're going to move through it quickly.

7 There's a notebook in front of you, but I'm
8 also going to put these things on the screen.

9 MR. LEE: Let's bring up the '775 patent.

10 Q. (By Mr. Lee) Dr. Marks, while you're pouring
11 your glass of water, Mr. Beck reminds me that I forgot
12 to ask you one question on your background.

13 You said that you were board-certified as a
14 doctor in three different areas.

15 A. That's correct.

16 Q. Would you tell the jury what those three
17 different areas are and how you become board-certified
18 in those areas, or how you became board-certified?

19 A. Yeah. Sleeping in hospitals.

20 So I -- I'm board-certified in three
21 specialties. Those specialties are internal medicine
22 anesthesiology, and intensive care medicine.

23 So as you probably know, there's a lot to
24 learn in order to take care of patients. And medical
25 school teaching, the first two years, are basically you

1 sit in a classroom, and you learn a lot of stuff that
2 has nothing to do with taking care of patients, frankly.
3 And then the next two years, you follow real doctors
4 around who are taking care of patients, but you're not
5 very involved in their care. But it's very -- it's very
6 exciting. I mean, it's why you're there.

7 In order to take care of patients, then you
8 must do a year of internship, which means you are an
9 apprentice doctor. You live in the hospital; really
10 live in the hospital like a hundred hours a week,
11 learning how to take care of patients.

12 But it really -- it really doesn't provide you
13 with adequate information to take care of any diseases
14 of any complexity. You can be a general practitioner.
15 But especially with the modern advances of medicine,
16 you're not very skilled.

17 And so there are specializations. And to
18 become specialized, you take additional training. So I
19 did three more years -- two more years of training in
20 internal medicine to take care of diseases like heart
21 attacks and bleeding ulcers.

22 And after I did those years of training, I
23 took a test administered by the American Board of
24 Internal Medicine, to prove that I had the requisite
25 knowledge, and then I became board-certified.

1 After that training, I realized that what I
2 liked taking -- I liked doing most was taking care of
3 very, very sick patients. And so I did a fellowship in
4 intensive care medicine.

5 So I spent a year taking care of critically
6 ill patients in the university hospital and at the
7 county hospital in the Intensive Care Unit. So patients
8 with heart attacks in the Coronary Care Units, patients
9 with respiratory failure on breathing machines in the
10 other Intensive Care Units.

11 And after that training -- I also took a test
12 and became board-certified in intensive care medicine.
13 After that training, I realized that what I really liked
14 was taking care of sick patients, but it was so intense
15 that I couldn't -- no one did it all their time. And so
16 I realized that the field of anesthesiology was very
17 similar to critical care medicine in terms of the skills
18 and the thinking required, but the patients generally
19 were not as sick.

20 So I then did two more years of training,
21 working and living in the hospital; took a test after
22 those years of training, passed that test, and became
23 board-certified in anesthesiology.

24 Q. Now, let's go to the '775 patent.

25 MR. LEE: And if I could have highlighted

1 the issuance date of July 4, 2006.

2 Q. (By Mr. Lee) You've heard testimony about
3 that, correct?

4 A. Yes, I have.

5 Q. And we've also heard testimony about the date
6 the application that led to this patent was first filed.

7 And what was that date?

8 A. July 18th, 2002.

9 Q. And if we go down a little bit, the jury has
10 seen this long list of related applications. And you've
11 seen that before, correct?

12 A. Yes, I have.

13 Q. Now, the jury has heard about the concept of a
14 prosecution history or a file history.

15 What is that?

16 A. A file history is the record of the
17 correspondence that goes back and forth between the
18 inventor -- excuse me -- and the Patent Office.

19 Q. Now, you're not a patent lawyer, correct?

20 A. No, I'm not.

21 Q. And you have no training in patent law,
22 correct?

23 A. That is correct.

24 Q. But you do have patents in your own right,
25 correct?

1 A. That is correct.

2 Q. Could you give the jury some idea of what the
3 volume is of the file histories for all of these
4 applications that eventually led to the '775 patent?

5 A. It is large. I think if you put it on the
6 floor, it would be taller than I am.

7 Q. How tall are you?

8 A. I tell my wife I'm 5-11, but she tells me I'm
9 only 5-10.

10 Q. Close enough.

11 What have you been asked to do in this case?

12 A. I have been asked to review the
13 patents-in-suit, all of the related U.S. application
14 data, the prior patents, and the correspondence from the
15 Patent Office, the file history.

16 Q. And have you been asked to address some
17 specific issues?

18 A. Yes. I have been asked to form opinions on
19 infringement and on validity.

20 Q. And have you focused on specific claims?

21 A. Yes, I have.

22 Q. Which claims?

23 A. 2, 3, 14, and 15.

24 Q. And you understand those are the claims that
25 Centocor says that we are infringing?

1 A. Yes, I do.

2 Q. Now, let's focus first on the issue of
3 validity. Can we do that?

4 A. Yes, we can.

5 Q. Have you formed an opinion as to whether
6 Claims 2, 3, 14, and 15 are valid?

7 A. Yes, I have.

8 Q. And what is your opinion?

9 A. My opinion is that those claims are not valid.

10 Q. Now, could you summarize your reasons so that
11 we can go through the reasons one by one?

12 A. Yes. There are three reasons.

13 The claims are not valid, because they are not
14 enabled. The claims are not valid, because there was no
15 written description. And the claims are not valid,
16 because they are anticipated by prior art.

17 Q. All right. And I'm going to come back to each
18 of those, but let me ask you about your second group of
19 opinions.

20 Have you also formed an opinion concerning
21 Centocor's claim that Abbott is infringing Claims 2, 3,
22 14, and 15 of the '775 patent?

23 A. Yes, I have.

24 Q. Do you have an understanding as a scientist as
25 to which party has the burden of proving infringement?

1 A. Yes, I do.

2 Q. And which party has the burden of proving
3 infringement?

4 A. Centocor does.

5 Q. And have you tried to reach a conclusion on
6 whether the information Dr. Adams and Centocor relies
7 upon satisfies that burden?

8 A. Yes, I have.

9 Q. And what is your opinion as to whether
10 Centocor has given the Ladies and Gentlemen of the jury
11 enough information to carry the burden of proving that
12 Abbott infringes?

13 A. They have not.

14 Q. All right. Now, I'm going -- before I get
15 into the specifics of your invalidity opinions, I want
16 to very quickly go through the background. The jury's
17 heard much of this before, so we'll go through it
18 quickly.

19 But there wasn't a whole lot yesterday about
20 the science that Dr. Salfeld testified to, so we'll do a
21 little bit of it, okay?

22 A. Yes.

23 Q. All right. Now, just remind us very quickly,
24 what is an antibody?

25 A. An antibody is a protein that each of our

1 bodies produces. In fact, we make many antibodies. And
2 the purpose of these molecules is to protect us from
3 disease-causing pathogens that we're continuously
4 exposed to. So it protects us against bacterial
5 infections. Antibodies protect us against viral
6 infections.

7 Q. Now, pathogens sounds like a medical term.
8 What's a pathogen?

9 A. A pathogen is a disease-causing organism, like
10 a bacteria or a virus.

11 Q. Do only humans make antibodies?

12 A. No. Many animals make antibodies.

13 MR. LEE: Now, could I bring up
14 Demonstrative Exhibit 26?

15 Q. (By Mr. Lee) And using this demonstrative,
16 could you explain to the jury a little bit further just
17 how antibodies work in our bodies?

18 A. Yes. So here we see the cartoon of the
19 Y-shaped antibody, and it's shown in red. And the
20 Y-shaped antibody is binding to the antigen blob, which
21 could be a bacteria or a virus.

22 And it binds in a very specific place. And
23 how tightly it binds determines how well it works. And
24 we call -- how sticky it binds, and we call that
25 property affinity.

1 And what the antibody is doing here is, it is
2 binding to the bacteria or virus and either keeping it
3 from working, keeping the virus from causing disease, or
4 eliminating it from the body.

5 Q. Now, you've been here when there's been
6 testimony about TNF-alpha, correct?

7 A. Yes, I have.

8 Q. And you're familiar with TNF-alpha, correct?

9 A. Yes, I am.

10 Q. When the body's working correctly, what is
11 TNF-alpha doing for us?

12 A. TNF-alpha is like an antibody, also a
13 molecule, made by our immune system, and it's like an
14 alarm clock. It wakes up the immune system.

15 So when the immune system senses a virus or a
16 bacteria, TNF is made -- it kind of wakes up or
17 stimulates the immune saying, hey, there's a problem
18 here. We need to start sending out some other parts of
19 the immune system to fight this bacteria.

20 Q. So it's like the -- it's like Paul Revere.
21 He's the one sounding the alarm to bring the troops
22 along.

23 A. Yeah. One of the alarm-sounders.

24 Q. Okay. And that's when it's working correctly.

25 A. That's correct.

1 Q. What happens when it's working incorrectly?

2 A. Yeah. So it's interesting, in human diseases,
3 many of the molecules we have in our body that we need
4 to be healthy, if there's too much of them, can also
5 cause disease.

6 And so there are a number of diseases where
7 there is either too much TNF, or the TNF is in the wrong
8 place, and it wakes up the immune system to attack our
9 own body, and disease is caused.

10 MR. LEE: Could we have DDX27, please.

11 Q. (By Mr. Lee) And using this demonstrative,
12 would you explain to the jury the concept of TNF-alpha
13 not working correctly in our bodies?

14 A. So what this demonstrative shows is that there
15 is too much TNF-alpha in the joint of this patient. It
16 is waking up the immune system, which is attacking the
17 joint, which you see shown here with the red
18 inflammation.

19 The immune system attacks the joint and causes
20 swelling, pain, discomfort, and ultimately destroys the
21 cartilage in the joint.

22 Q. Now, you'll see that there are portions -- I'm
23 not tall enough to reach them -- of the TNF-alpha
24 antibodies that look like -- see what I'm pointing to
25 here?

1 A. I see -- yes. I see the TNF molecule there.

2 Q. And there are little portions sticking out.

3 Do you see those?

4 A. Well, I need bifocals. Yes, I see them.

5 Q. Now, what is the purpose of an anti-TNF-alpha
6 antibody?

7 A. So the purpose of an anti-TNF-alpha antibody
8 is to bind to the right place on TNF so that it stops it
9 from working, that it prevents its ability to wake up
10 the immune system and cause disease.

11 Q. So if we go back in time to the 1980s and
12 1990s, what were the characteristics that scientists
13 were looking for if they were going to have a useful --
14 therapeutically useful anti-TNF-alpha antibody?

15 A. Right. So it's important that the antibody
16 bind to the right place on TNF-alpha in order to keep it
17 from working.

18 So antibodies bind in many, many places on
19 their target; in this case, TNF, but many of those
20 places will not keep the TNF from working. So it's
21 critical that it binds to the right place.

22 It also needs to bind very tightly, because if
23 it doesn't bind very tightly, then it will not stop the
24 TNF from working.

25 And then it's very important the antibody look

1 as human as possible, so that when we give it to humans,
2 it's not recognized as a foreign protein and doesn't
3 cause the immune system to attack the antibody.

4 Q. Now, the term affinity refers to which of
5 those qualities?

6 A. It's the stickiness. It's how tightly the
7 antibody sticks to TNF.

8 Q. And do you want an antibody with high affinity
9 or low affinity?

10 A. High affinity.

11 Q. And are there ways to measure affinity?

12 A. There are many, many ways to measure affinity.

13 Q. And have those methods changed over time?

14 A. Yes, they have.

15 Q. Are you familiar with a concept of
16 neutralization?

17 A. Yes, I am.

18 Q. And what does neutralization mean?

19 A. Neutralization describes this property of
20 keeping the TNF from working so that when TNF is
21 neutralized, TNF doesn't work.

22 Q. And in order to have a therapeutic product,
23 you want to have an antibody that both binds with high
24 affinity and works, correct?

25 A. That's correct.

1 Q. And the antibody -- the fully human antibody
2 that you made in 1991, what was it missing?

3 A. It was missing the affinity property. It was
4 not of adequate affinity. And we don't know whether it
5 neutralizes or not. We did not test whether it
6 neutralized.

7 Q. And it took you three years of work to get to
8 the point where you had it and could determine that it
9 was not high enough affinity?

10 A. Correct.

11 Q. All right. Now, let me bring up
12 Demonstrative -- DDX28, which describes different types
13 of antibodies.

14 Now, the jury's heard about this before, but
15 to just put us all back on an even playing field, would
16 you describe to us, using this demonstrative, the
17 different types of antibodies?

18 A. Yes. So this demonstrative shows the four
19 types of antibodies that have been used to treat human
20 diseases.

21 Q. Now, let's start with the first.

22 What was the first antibody that was developed
23 and used in an effort to treat human diseases?

24 A. These were antibodies made in mice, and they
25 were completely mouse in sequence, which means in terms

1 of how they -- what they looked like to a human immune
2 system, they were very foreign. They -- they were mouse
3 antibodies.

4 Q. Now, Dr. Le, in his videotaped testimony used
5 the term murine. What does the word murine mean?

6 A. Murine is a fancy science name for a mouse.

7 Q. Now, how are mouse antibodies created?

8 A. Yes. So I believe we have a demonstrative.

9 Q. Yes.

10 MR. LEE: Let's bring up DDX29.

11 A. Right. So in order to make antibodies from
12 mice, we take what we want the antibodies to be made to,
13 in this case, TNF, and we inject it into the mouse. In
14 fact, we inject it multiple times.

15 And human TNF looks very different than mouse
16 TNF, and so the mouse recognizes TNF -- human TNF as
17 foreign, and it makes antibodies to it to try to
18 eliminate it and neutralize it.

19 Q. (By Mr. Lee) And what can you do once the
20 mouse has generated anti-TNF-alpha antibodies?

21 A. Yes. So most of the B-cells that make
22 antibodies are located in the mouse spleen. And the
23 spleen is that organ that sits under here (indicating)
24 in us.

25 And what you do is you take the spleen

1 surgically out of the mice, you isolate the B-cells from
2 the mouse, and then you mix them or fuse them with a
3 cancer cell so that they will live forever. And then
4 you can test the antibodies for whether they have
5 properties that bind and neutralize TNF.

6 Q. Now, just so we all can understand it, there's
7 been discussion about cancer cells and hybridomas,
8 correct?

9 A. That's correct.

10 Q. One of the reasons that cancer cells are a
11 problem, as far as when we get cancer, is they are cells
12 that rapidly re-create themselves and grow and expand
13 and cause problems, correct?

14 A. That's correct.

15 Q. But if you use the cancer cell in a laboratory
16 with something that you want it to re-create, you could
17 use it to sort of be a little factory and continue to
18 produce more and more and more of what you want.

19 A. That's correct.

20 And that's what a hybridoma is. Hybrid means
21 a combination of two or more things. And so a hybridoma
22 cell contains the mouse-antibody-producing part in a
23 cancer cell that can grow forever.

24 Q. Now, are mouse antibodies used to treat
25 long-term human diseases?

1 A. No, they are not.

2 MR. LEE: Could I have DDX31, please.

3 Q. (By Mr. Lee) Using this demonstrative, could
4 you explain to the jury just why mouse antibodies can't
5 be used long term to treat human diseases?

6 A. Yes, I can.

7 So in this demonstrative, we see the mouse
8 antibody in red. And as I said, the mouse antibody is
9 complete -- looks completely different than the human
10 antibody to the human immune system.

11 It's recognized as foreign. Our body makes
12 antibodies to it, which are shown in green, and they
13 bind to and either -- and keep the mouse antibody from
14 working and also eliminate the mouse antibody from the
15 body.

16 And in a certain number of patients, this
17 interaction will also cause life-threatening reactions,
18 like anaphylactic shock, which is a type of shock where
19 the cardiovascular system, the heart collapses.

20 Q. Now, were any mouse antibodies to TNF-alpha
21 invented or created?

22 A. Yes, there were.

23 Q. Can you give us a couple of examples.

24 A. MAK195 and A2.

25 Q. Now, there's been some suggestion by Centocor

1 that Centocor was the first to identify TNF-alpha as a
2 candidate for antibodies.

3 Did you hear that?

4 A. Yes, I did.

5 Q. Which of these mouse antibodies, MAK195 and
6 A2, came first?

7 A. MAK195.

8 Q. What is MAK195?

9 A. MAK195 is a high affinity, neutralizing
10 antibody to TNF-alpha.

11 Q. And who made MAK195?

12 A. Abbott did.

13 Q. And was it a predecessor of Abbott?

14 A. Yes. It was BASF.

15 Q. And who was the person who made this
16 invention?

17 A. Jochen Salfeld, who you heard from yesterday.

18 Q. Jochen --

19 A. I'm sorry. It was Achim Noller (sic).

20 Q. Moller?

21 A. Moller. Sorry. Achim Moller.

22 Q. And Achim Moller was the creator or the
23 inventor of MAK195.

24 A. That's correct.

25 Q. Did he apply for a patent?

1 A. Yes, he did.

2 Q. When did he make this invention?

3 A. In 1986.

4 Q. Now, you also mentioned A2, correct?

5 A. That's correct.

6 Q. Dr. Le just testified about A2, correct?

7 A. Yes, he did.

8 Q. Another mouse antibody?

9 A. That's correct, a mouse antibody.

10 Q. Done in collaboration with Centocor?

11 A. Done in collaboration with Centocor.

12 Q. When was it done?

13 A. 1989.

14 Q. Both were high affinity antibodies with TNF as
15 the target, correct?

16 A. That's correct.

17 Q. Both before Centocor did its chimeric antibody
18 work, correct?

19 A. That's correct.

20 MR. LEE: Can I have Demonstrative
21 Exhibit 17 on the screen, please.

22 Q. (By Mr. Lee) Now, we're going to fill this in
23 as we go, but for just the mouse antibodies, could you
24 identify the portions of the chronology that concern the
25 mouse antibody made by Dr. Moller and the mouse antibody

1 made by Centocor.

2 A. Yeah. They're in the far left of the big
3 timeline. And so we can see on the top, in 1986, that
4 was the MAK195, the mouse antibody, produced by
5 Dr. Moller at BASF.

6 And then on the bottom, in 1989, we see the
7 Centocor mouse antibody, A2.

8 Q. Now, let's go back to Demonstrative Exhibit
9 28, if we could, and let's go to the second category of
10 antibodies.

11 That is chimeric, correct?

12 A. That is correct.

13 Q. And just remind us, a chimeric antibody is?

14 A. So a chimeric antibody is an antibody where
15 only the variable regions or the part of the antibody
16 that actually binds to TNF is mouse, and genetic
17 engineering techniques are used to make the rest of the
18 antibody, the constant region human.

19 MR. LEE: And could we have Demonstrative
20 Exhibit 32.

21 Q. (By Mr. Lee) Does the patent itself that's in
22 the jurors' notebooks describe and define what a
23 chimeric antibody is?

24 A. Yes, it does.

25 Q. What does it say?

1 A. It says that chimeric antibodies are
2 molecules, different portions of which are derived from
3 different animal species.

4 MR. LEE: Could we have Demonstrative 33,
5 please.

6 Q. (By Mr. Lee) Now, I think you've just touched
7 on this, but using 33, just remind us of what part's
8 human and what part's mouse, rodent, or otherwise.

9 A. All right. So the variable region or the part
10 of the antibody that binds to TNF is rodent or mouse,
11 and the rest of the antibody, the constant region or the
12 stem is human.

13 Q. Now, were you here when Dr. Ghayeb referred
14 to the sequences for the portions that are variable at
15 the very tip?

16 A. Yes, I did.

17 Q. So if he just said, well, in our patent, we
18 describe the particular sequences for these tips -- do
19 you remember that?

20 A. Yes, I do.

21 Q. Are those sequences the same as Humira?

22 A. No. They're very different.

23 Q. Okay. Now, this is called a variable region
24 for what reason?

25 A. Because the sequence varies between different

1 antibodies. And the reason it varies is so that the
2 antibody can recognize different antigens, yeah.

3 Q. And is it important?

4 A. It's very important. It's the part of the
5 antibody that determines what the antibody binds to.
6 Different variable regions bind to different proteins.
7 Some will bind TNF; some will bind bacteria; some will
8 bind viruses.

9 So it's this variability of the sequence of
10 the variable region that determines what the antibody
11 sticks to.

12 Q. You were here when Dr. Salfeld described this
13 as a little bit like a lock and a key?

14 A. That's correct.

15 Q. And does a variable region tell you whether
16 you have the right key or not?

17 A. The variable region is the key in the lock and
18 key.

19 Q. All right. And if you have the wrong key,
20 you're not going to open the door.

21 A. That's correct.

22 Q. Now let's go to the constant region.

23 What is it -- why is it called a constant
24 region? Why is it important?

25 A. It's called a constant region, because its

1 sequence is very similar or identical between different
2 antibodies. It is the Y -- it is the stem of the
3 Y-shaped molecule, and it provides structure and also
4 has other functions in the body.

5 Q. Now, who developed the first chimeric
6 antibody?

7 A. To TNF-alpha?

8 Q. To TNF-alpha. I'm sorry. To TNF-alpha.

9 A. Yes. Centocor did.

10 Q. And when did Centocor develop that?

11 A. They developed that in 1990, I believe.

12 Q. So let's go back to our timeline.

13 MR. LEE: If I could have Demonstrative
14 17 again.

15 Q. (By Mr. Lee) Just to put everything in
16 context, do you see -- this one I can reach -- in 1990,
17 Centocor developed the chimeric antibody?

18 A. Yes, that's correct.

19 Q. Now, you testified that a mouse antibody
20 cannot be used for long-term treatment of humans,
21 correct?

22 A. That's correct.

23 Q. And that's because of the possibility of the
24 generation of an immune response, correct?

25 A. It's not just possible; it happens. I mean,

1 no one -- no pharmaceutical companies develop mouse
2 antibodies as drugs anymore. They cannot be given for
3 the long term.

4 Q. Now, did the creation of chimeric antibodies,
5 which was part mouse/part human, solve entirely the
6 problem?

7 A. No, it did not.

8 Q. Why did it not solve entirely the problem?

9 A. It did not solve the problem, because you have
10 the variable regions that are still mouse. And the
11 variable regions are about 25 percent of the antibody.
12 And in some patients, those are, because they're mouse,
13 recognized as foreign, and the body mounts an immune
14 response.

15 So in 1990, in the early '90s, this was a very
16 good way of making antibodies that could at least be
17 administered many, many times in humans, and in many
18 humans, there is not an immune response.

19 But let me be perfectly clear. Ultimately,
20 better ways of making antibodies were developed that
21 made them more human in their sequence. And today a
22 pharmaceutical company developing a new antibody drug
23 would not make a chimeric antibody.

24 Q. How much -- you've heard of cA2, correct?

25 A. Yes, I have.

1 Q. Also called Remicade?

2 A. Yes, I have.

3 Q. How much of Remicade is human, and how much of
4 it is mouse?

5 A. About 25 percent mouse; about 75 percent
6 human.

7 MR. LEE: Could we go back to
8 Demonstrative 28, please.

9 Q. (By Mr. Lee) Let's go to the third category of
10 antibody, humanized. What is a humanized antibody?

11 A. So a humanized antibody uses technology
12 developed by my Ph.D. supervisor, Dr. Greg Winter, in
13 which it became possible to make more of -- make the
14 variable region largely but not completely human in
15 sequence.

16 So a humanized antibody has much less mouse
17 sequence in it than a chimeric antibody.

18 MR. LEE: Could we have Demonstrative 34,
19 please.

20 Q. (By Mr. Lee) What's depicted on Demonstrative
21 34, and can you use it to explain the concept of the
22 humanized antibody.

23 A. Yes, I can.

24 So in Demonstrative -- in this demonstrative,
25 what we see is that the parts of the mouse antibody that

1 actually touch or make contact with the antigen, would
2 make contact with TNF, have been put on a human variable
3 region.

4 And so most of the variable region is human,
5 and just these parts of the variable region that touch
6 the antigen are mouse, and then the entire constant
7 region is human.

8 Q. And what is the part, the small part that
9 remains mouse that is actually touching TNF?

10 A. Yeah. We scientists always use big words, so
11 we call those the complementarity determining region
12 because they complement the antigen, and we abbreviate
13 that, because those are big words, with CDR.

14 Q. Is that just the key?

15 A. It's a large part of the key. You can think
16 of it -- it's like the teeth on the key that go into the
17 lock. And the rest of the variable region kind of forms
18 the backbone of the key that actually holds the teeth.
19 So it does have a role to play, but just think of it as
20 the teeth on the key.

21 Q. And it is the complement -- is the CDR
22 important?

23 A. Yes, it is.

24 Q. Now, are you familiar with any humanized
25 antibodies to TNF?

1 A. Yes, I am.

2 Q. Can you give the jury an example of a
3 humanized antibody to TNF that was developed by
4 scientists.

5 A. Yes. There's an antibody called CDP571 that
6 was developed by scientists at Celltech.

7 Q. And very generally, can you describe what
8 CDP571 is or was.

9 A. Yes. CDP571 is a high affinity, neutralizing,
10 humanized antibody to TNF-alpha.

11 MR. LEE: Let's go back to Demonstrative
12 Exhibit 17, if we could.

13 Q. (By Mr. Lee) Could you place for the jury the
14 development of CDP571?

15 A. Yes. CDP571 was invented by Adair and his
16 colleagues in 1992.

17 Q. And they applied for a patent, correct?

18 A. Yes, they did.

19 Q. Now, you'll see that I put under the
20 chronology February 1994.

21 A. Yes, I do.

22 Q. And you were here when Ms. Elderkin said in
23 her opening, this was a key date, correct?

24 A. Yes, I was.

25 Q. Now, everything we've described so far has

1 occurred before February 1994, correct?

2 A. Yes, it has.

3 MR. LEE: Let's go back to Demonstrative
4 28.

5 Q. (By Mr. Lee) The fourth type of antibody is
6 what?

7 A. Fully human antibodies.

8 Q. Now, in the demonstrative -- you helped us
9 prepare this demonstrative?

10 A. Yes, I did.

11 Q. The -- there's a mouse at the top leading to
12 the three types of antibodies, but then there are people
13 at the bottom leading to the fully human.

14 A. That's correct.

15 Q. Could you explain why that -- you've depicted
16 it this way?

17 A. Yes. Because all of the types of antibodies
18 shown at the top use -- have at least part of them
19 consisting of a sequence that was derived from a mouse;
20 whereas fully human antibodies do not have any sequence
21 that was derived from a mouse; they have sequence that
22 was derived from humans.

23 Q. Now, you were asked if you were working in the
24 field in the 1980s and 1990s when scientists decided to
25 pursue fully human antibodies, correct?

1 A. Yes, I was.

2 Q. So based upon your work, being there, would
3 you tell the jury why were scientists trying to create
4 fully human antibodies?

5 A. So fully human antibodies are the Holy Grail
6 of people who developed antibody-based drugs. And the
7 reason they're the Holy Grail is because they are what
8 our bodies make. They are either identical or as close
9 as can be to the antibodies we have in our bodies.
10 And, therefore, the thinking is that these antibodies
11 would be best tolerated as drugs. They would be least
12 likely to elicit an immune response.

13 Q. And who developed the first fully human
14 antibody to anti -- to TNF-alpha?

15 A. Abbott did.

16 Q. And that's the antibody that Dr. Salfeld
17 described yesterday?

18 A. Yes, it is.

19 Q. And was there a name for it?

20 A. It was called D2E7 in the laboratory and came
21 to be known by Humira, its trade name.

22 MR. LEE: And could we have Demonstrative
23 Exhibit 17 back on the screen, please.

24 Q. (By Mr. Lee) When was D2E7 made?

25 A. In 1995, the summer of 1995.

1 Q. So you'll notice that I've put on the screen
2 as well the July 2002 patent date --

3 A. Yes, I see it.

4 Q. -- that we discussed a little earlier?

5 A. Yes.

6 Q. Now, at the time --

7 MR. LEE: Oh, I'm sorry. Withdrawn, Your
8 Honor.

9 Q. (By Mr. Lee) In 1995 --

10 MR. LEE: Can we bring that down. Thank
11 you.

12 Q. (By Mr. Lee) In the summer of 1995, when
13 Abbott was successful in making a fully human
14 anti-TNF-alpha antibody, were any other neutralizing,
15 high affinity, fully human anti-TNF-alpha antibodies
16 publicly disclosed?

17 A. Not that I'm aware of.

18 Q. All right. Using our timeline, when was
19 Humira or D2E7 introduced to the U.S. market?

20 A. Humira was approved by the FDA, I learned
21 today, on New Year's Eve, actually, in 2002.

22 Q. Now, at that time, were there any other high
23 affinity, neutralizing, fully human antibodies to
24 TNF-alpha on the market?

25 A. No, there were not.

1 Q. In fact, Dr. Marks, were there any fully
2 human, high affinity, neutralizing antibodies available
3 in the U.S. market to treat any disease?

4 A. No. Humira was the first fully human antibody
5 approved by the FDA.

6 Q. You were here when Mr. Scodari mentioned both
7 Remicade and Humira?

8 A. Yes, I was.

9 Q. He described both as a dramatic innovation?

10 A. Yes, he did.

11 Q. Given that you were there at the time, was the
12 discovery of Humira a dramatic invention?

13 A. Yes, it was. And I think for those of us
14 working in the field at that time and who had been
15 working there for a long time, it really validated the
16 work that we had been doing to bring this type of
17 antibody into clinical practice.

18 Q. And were you familiar with the different
19 techniques that scientists tried to make this happen?

20 A. Yes, I am.

21 Q. And were you familiar with those techniques
22 back at that time?

23 A. Yes, I was.

24 MR. LEE: Let's bring up Demonstrative
25 Exhibit 35.

1 Q. (By Mr. Lee) And can you tell us what you've
2 listed on this demonstrative.

3 A. So I've described in general terms the three
4 ways that scientists tried -- used to try and make human
5 antibodies.

6 Q. Now, the first one says naturally occurring
7 from human B-cells, Casali method. Why have you
8 described it that way?

9 A. So these are a variety of different but
10 related technologies that all rely on taking from human
11 beings, usually, by drawing blood, the antibody-
12 producing B-cells and then using different approaches to
13 stabilize and grow the B-cells outside the body and test
14 the antibodies produced by them for their ability to
15 bind to TNF.

16 Q. Now, you described it as the Casali method.
17 Why is that?

18 A. Because Dr. Casali, whose testimony you heard,
19 was one of the pioneers of this technology, one of the
20 people who developed it.

21 Q. And how did scientists, back at this time, in
22 the '80s and the '90s, attempt to use B-cells to
23 identify antibodies?

24 A. Yes. So as I briefly said, they would
25 identify -- so in some instances, for example, if they

1 wanted to make antibodies to a bacteria or a virus, or
2 as you heard Dr. Casali say, DNA, they would take
3 patients who had been infected with these diseases or
4 who had an autoimmune disease, like Lupus, and these
5 patients would at least have in their bloodstream
6 B-cells producing antibodies.

7 And they would because they had been exposed
8 to something foreign, and their immune system would make
9 antibodies, or their immune system was attacking their
10 body and would make antibodies.

11 So their blood was enriched for B-cells making
12 antibodies. And then the scientists would draw the
13 blood and then try to grow the B-cells outside of the
14 body and test them for producing antibodies.

15 Q. Now, you can't cut the spleen out of a human
16 like you would with a mouse, correct?

17 A. No.

18 Q. Not ethically.

19 A. Not for scientific purposes.

20 Q. And so you're left with drawing blood and
21 seeing what you can get from the blood?

22 A. Yes. And as I had said earlier, most of the
23 antibody-producing cells are in the spleen or they're in
24 the bone marrow. They're not actually circulating in
25 the bloodstream.

1 Q. Now, using this Casali method, were there
2 attempts back in the 1980s and 1990s to make a high
3 affinity, neutralizing antibody to TNF using the Casali
4 method?

5 A. Yes, there were.

6 Q. And are you familiar with those?

7 A. Yes, I am.

8 MR. LEE: Could we have the timeline,
9 Demonstrative 17, back on the screen.

10 Q. (By Mr. Lee) Let's first talk about the Casali
11 method. Explain what that effort was with Abbott.

12 A. Yes. So Dr. Casali collaborated with Abbott
13 in what I believe was a funded project to use his
14 technology to attempt to make high affinity,
15 neutralizing antibodies to human TNF-alpha.

16 Q. And when did that project begin?

17 A. That project, as you've heard from Dr. Casali,
18 began in 1991.

19 Q. Was it successful?

20 A. No, it was not successful, despite the two
21 years of work.

22 Q. Now, are you familiar with any other efforts
23 before February of 1994 to use B-cells to make a high
24 affinity, neutralizing anti-TNF-alpha antibody?

25 A. Yes, I am.

1 Q. Who made that other effort?

2 A. So that effort occurred at Centocor. They
3 studied an antibody, as you heard from Dr. Le, produced
4 in the laboratory at Sloan-Kettering. That antibody
5 call 7.T.1 went to Dr. Le, who tested it, and found that
6 it was also non-neutralizing.

7 Q. Just so we're clear, 7.T.1 is the name of a
8 fully human antibody --

9 A. That's correct.

10 Q. -- that was sent to Dr. Le --

11 A. That's correct.

12 Q. -- one of the named inventors --

13 A. That's correct.

14 Q. -- before February of 1994?

15 A. That's correct.

16 Q. He tested it?

17 A. Yes.

18 Q. Was he successful?

19 A. No. The antibody did not neutralize TNF.

20 MR. LEE: Now, could I have the full
21 chronology again?

22 Q. (By Mr. Lee) Focusing on this February 1994
23 date, did anybody anywhere in the world use B-cell
24 technology to produce a fully human anti-TNF -- high
25 affinity, neutralizing anti-TNF-alpha antibody?

1 A. No, not that I'm aware of.

2 Q. In fact, based upon your more than quarter
3 century in the field, as of today, as of 2009, has
4 anybody used the B-cell approach to produce a high
5 affinity, neutralizing anti-TNF-alpha antibody?

6 A. And I think you're making me older than I am.
7 I think I've only had 20 plus years' experience in the
8 field. But the answer to the question is no.

9 Q. And why not?

10 A. So this was very promising and tantalizing
11 technology in the late 1980s and late 1990s. And as I
12 said, to scientists and drug companies, a fully human
13 antibody is the Holy Grail.

14 So a lot of technologies were simultaneously
15 developed, and at their early stages, they looked
16 really, really promising, and we got very, very excited.
17 And then a number of them turned out not to be able to
18 do what we originally thought they could do. And this
19 is one of those technologies.

20 So there turned out to be a number of
21 significant hurdles.

22 So in the case of making antibodies to
23 TNF-alpha, unlike a mouse, you can't inject humans with
24 TNF-alpha to get them to make antibodies. And the
25 reason is, it's not safe. TNF causes disease.

1 In addition, TNF is one of our own proteins.
2 Our bodies will not recognize it as foreign, and
3 generally speaking, we will not make antibodies to it.
4 Our B-cells will not make antibodies to it.

5 In the rare instances where they do, these are
6 very low affinity, what are called, IgM antibodies.
7 So there are basically no B-cells in our body making
8 usable antibodies to TNF-alpha.

9 And, therefore, when you draw the blood, which
10 would contain very few antibody-producing B-cells
11 anyway, you just -- and test them, you just don't get
12 B-cells that produce antibodies with the necessary
13 properties to TNF-alpha or, in fact, almost all other
14 human proteins.

15 So, in fact, this technology has never to this
16 date been used to produce an antibody that was licensed
17 by the Food & Drug Administration.

18 MR. LEE: Let's go back to Demonstrative
19 35 and go through the second method.

20 Q. (By Mr. Lee) What's the second method you've
21 listed?

22 A. Antibody phage display.

23 Q. And this is the technology on which you are
24 one of the named inventors, correct?

25 A. That's correct.

1 Q. And again, briefly, what is phage display?
2 Just remind us.

3 A. So you -- you heard a little bit earlier about
4 phage display from Dr. Salfeld. So phage display is a
5 way to make human antibodies in the test tube entirely
6 outside of the body and without having to inject humans
7 with anything, so you don't have to inject with TNF.
8 And what we do to make phage antibodies is, we take
9 human volunteers, who let us draw their blood, and we
10 take their B-cells, and then we take the DNA that
11 encodes all the antibodies that could be produced, and
12 we take it into the test tube, and we reassort it, and
13 we basically make what we call a library of antibodies.
14 And we call this a library, because like your local
15 library that has a lot of books, this is an antibody
16 library, and it has a lot of antibodies.

17 But unlike your local library, which might
18 have -- I don't know -- thousands of books, these
19 antibody libraries can have millions to billions of
20 different antibodies.

21 Q. Now, you told us before phage display has been
22 used to produce how many successful therapeutic
23 projects -- products?

24 A. Only one that's been licensed by the Food &
25 Drug Administration.

1 Q. And that's Humira?

2 A. That's correct.

3 Q. Now, was phage display alone sufficient to
4 create Humira?

5 A. No, it was not.

6 Q. Were there other inventions required by people
7 other than you and your colleagues?

8 A. Yes.

9 Q. And did you participate in those?

10 A. No, I did not.

11 MR. LEE: Now, if I could have the
12 chronology back on the screen, and highlight the date of
13 Abbott making the fully human antibody.

14 Q. (By Mr. Lee) December of 1995?

15 A. Yes.

16 Q. Now, as of that date, the summer of 1995 had
17 any other company created a high affinity, neutralizing
18 antibody to TNF using phage display?

19 A. No, not that I'm aware of.

20 Q. To this day, has any other company done that?

21 A. No, not that I'm aware of.

22 Q. And, in fact, sir, before the summer of 1995,
23 are you familiar with an effort to create a fully-human
24 anti-TNF-alpha antibody by phage display, which was
25 unsuccessful?

1 A. Yes. Yes, I am.

2 Q. What effort was that?

3 A. So we made a -- we made a number of antibodies
4 to TNF-alpha in Greg Winter's lab. We measured the
5 affinity of at least one of them, and it was a low
6 affinity.

7 Both were very early days of phage display
8 technology. And we know from the studies of affinities
9 of any other antibodies to other antigens, that they
10 were of low affinity.

11 And we did not test the TNF-alpha antibodies
12 for neutralization.

13 Q. Now let's go back to our chart with the three
14 methods.

15 A. Yes.

16 Q. What's the third method?

17 A. So the third method uses transgenic mice.

18 Q. Now, are you familiar with anyone who's used
19 transgenic mice to produce a fully human anti-TNF-alpha
20 antibody?

21 A. Yes, I am.

22 Q. And who did that?

23 A. Centocor did that.

24 Q. And when did Centocor do that?

25 A. I believe they did that in 1997 or 1998.

1 MR. LEE: Could I have our timeline on
2 the screen, please.

3 Q. (By Mr. Lee) When did transgenic mice
4 technology begin to become available?

5 A. About in the middle 1990s.

6 Q. Now, in the February 1994 application, is
7 there any mention of transgenic mice?

8 A. No, there's not.

9 Q. In the July 2002 application, is there any
10 mention of transgenic mice?

11 A. No, there's not.

12 Q. Now, using the timeline, when did Centocor
13 begin its human antibody project?

14 A. In 1997.

15 Q. And were you here when Dr. Ghrayeb said they
16 were successful about a year later?

17 A. Yes, I was.

18 Q. Did Centocor file a patent application on its
19 new fully human antibody?

20 A. Yes, they did.

21 Q. And approximately when?

22 A. I believe that was in July in 2002.

23 Q. And you were here when --

24 A. Sorry. I was not -- I don't recall when the
25 patent was filed.

1 Q. All right. When we come back to it, I'll show
2 you the patent.

3 A. Okay.

4 Q. Now, let's turn now to the specific reasons
5 for your validity opinion. Can we do that?

6 A. Yes, we can.

7 Q. Now, I think the first thing you mentioned was
8 enablement, correct?

9 A. That's correct.

10 Q. The second was written description.

11 A. That's correct.

12 Q. And the third was what you called
13 anticipation.

14 A. That's correct.

15 Q. Now, those are lawyers' terms, correct?

16 A. They certainly are.

17 Q. And you understand that on those legal issues,
18 the jury will be guided by what His Honor instructs
19 them, correct?

20 A. Yes, I do.

21 Q. As you understand them, are they independent
22 reasons for reaching your opinion?

23 A. Yes, they are.

24 Q. All right.

25 MR. LEE: Now, let's go back to the '775

1 patent, PX1, and put it on the screen.

2 Q. (By Mr. Lee) Now, you told the jury earlier
3 that July 2002 was the filing date that's described on
4 the patent, correct?

5 A. That's correct.

6 Q. But you were here when Ms. Elderkin told the
7 jury that, well, actually, Centocor is relying upon a
8 February 1994 filing date, correct?

9 A. That's correct.

10 Q. And do you have an understanding of why
11 Centocor wants to get back to February 1994?

12 A. Well, if they relied on -- my understanding
13 is, if they relied on the July 2002 date, then the fully
14 human antibody Humira had already been invented, and if
15 it met the scope of the --

16 MS. MULLIN: Objection, Your Honor.

17 THE COURT: Yes. What's your objection?
18 State it.

19 MS. MULLIN: My objection is that they do
20 not have a prior invention defense, and he has not given
21 any opinions in his report --

22 THE COURT: Sustained.

23 MS. MULLIN: -- that would support the
24 opinion he's given.

25 MR. LEE: I only asked him about the

1 patent, Your Honor.

2 THE COURT: I sustained the objection as
3 to the question.

4 MR. LEE: Okay.

5 Q. (By Mr. Lee) Now, the patent -- let's go back
6 to the timeline.

7 A. Okay.

8 Q. When was the Salfeld patent issued?

9 A. In July of 2000.

10 Q. So that would be before the July 2002 filing
11 date, correct?

12 A. That's correct.

13 Q. But in any event, you've been here when
14 Centocor has said that it's relying upon the February
15 1994 date, correct?

16 A. That's correct.

17 Q. Now, for the enablement and written
18 description requirements, as you formulated your
19 opinions, is it your understanding that the enablement
20 requirement applies to the 1990 -- February 1994
21 application?

22 A. That's correct.

23 Q. Is it your understanding that the written
24 description requirement applies to the February 1994
25 application?

1 A. That's correct.

2 Q. All right. Now, have you undertaken to
3 determine whether those 1994 applications comply with
4 each of those requirements?

5 A. Yes, I have.

6 Q. All right.

7 MR. LEE: Now, let's bring up the claims
8 the jury is going to be asked to consider, and bring up
9 Claims 1 and 2 first from PX1.

10 Q. (By Mr. Lee) And I just want to focus you on
11 Claims 1 and 2.

12 Claim 2 is dependent upon Claim 1, correct?

13 A. Correct.

14 Q. So that you have to have all of the
15 limitations of Claim 1 and Claim 2 to figure out what
16 Claim 2 requires, correct?

17 A. That's correct.

18 Q. And you'll see, at the very bottom of Claim 2,
19 there's a requirement of a human variable region,
20 correct?

21 A. That's correct.

22 Q. Does a chimeric antibody have a human variable
23 region?

24 A. No, it does not.

25 Q. And is the same true for Claims 3, 14, and 15;

1 they all require a human variable region?

2 A. That's correct.

3 Q. And a chimeric antibody would not have that,
4 correct?

5 A. That's correct.

6 Q. Now, do the 1994 applications contain any
7 information on experiments, tests, results for any type
8 of antibody to TNF-alpha?

9 A. Yes, they do.

10 Q. And for what type of antibody do they have
11 tests?

12 A. For chimeric antibodies.

13 Q. And is there a specific chimeric antibody
14 described in all of those tests?

15 A. CA2.

16 Q. Are there tests for any others?

17 A. No, there are not.

18 Q. How many examples were there in the 1994
19 applications?

20 A. I believe there are 26 or 28.

21 Q. And were any of them for a fully human
22 antibody?

23 A. No, they were not.

24 Q. All right. Now, let's turn to the specifics
25 of your opinion concerning enablement.

1 You've told us you're not a lawyer, and this
2 is a legal concept, correct?

3 A. That's correct.

4 Q. But so the jury can understand how you
5 formulated your opinion, what is your understanding of
6 what enablement requires?

7 A. So enablement would require that the patent
8 teach someone of ordinary skill in the art how to make
9 or use human antibodies without undue experimentation.

10 Q. Now, you've used the term ordinary skill in
11 the art. That's also a legal concept?

12 A. It is.

13 Q. And what do you understand the qualifications
14 of a person of ordinary skill in the art to be as of
15 February 1994?

16 A. A person of ordinary skill in the art would
17 have a Ph.D. in molecular biology or a related
18 discipline and several years of experience in the field.

19 Q. Now, for that person, have you formed an
20 opinion as to whether the asserted claims, 2, 3, 14, and
21 15, were enabled in February 1994; that is, have you
22 formed an opinion as to whether those applications
23 taught that person how to make and use fully human
24 antibodies?

25 A. Yes, I have.

1 Q. And what is your opinion?

2 A. They do not.

3 Q. And why?

4 A. Because there is absolutely no teaching in
5 those -- in that application on how to either make or
6 how to use human antibodies.

7 Q. And in order for them to make that teaching,
8 in order to teach how to fish, to use my analogy, what
9 would the specification have had to teach someone of
10 ordinary skill in the art?

11 A. It would have had to have shown them or
12 provide instructions on how to make human antibodies.

13 Q. Now, in February 1994, what was the state of
14 technology for engineering human antibodies in general?

15 A. Yeah. I think, as the jury has heard from
16 several of the witnesses, these are very, very early
17 days in the technologies used to make fully human
18 antibodies.

19 There were a lot of promising technologies
20 that were out there that promised to be able to make
21 human antibodies. Some of them ultimately proved
22 capable; many of them did not.

23 All of them were -- ultimately required
24 additional inventions, additional experimentation in
25 order for them to be used to make antibodies with useful

1 therapeutic properties.

2 Q. Now, 1994 --

3 THE COURT: Mr. Lee, let's break it right
4 here for our morning break.

5 MR. LEE: Okay.

6 THE COURT: Ladies and Gentlemen, we'll
7 take our morning break. Do not discuss this matter, and
8 I'll see you back at 10:30, 10:30.

9 COURT SECURITY OFFICER: All rise.

10 (Jury out.)

11 THE COURT: Court's in recess until
12 10:30.

13 MR. SAYLES: Your Honor, Ms. Mullin had
14 something she wanted to bring up.

15 THE COURT: All right. Y'all approach
16 the bench.

17 Court's in recess, but counsel approach.

18 (Bench conference.)

19 MS. MULLIN: Okay. There have been three
20 things that have come up so far that may require
21 instructions to the jury.

22 One is that the witness keeps referring
23 to Humira being licensed by the FDA, and that's
24 completely inaccurate that the FDA has any authority to
25 license.

1 MR. LEE: Well, I'll clear that up. I'll
2 clear that up.

3 MS. MULLIN: Okay. On the prior
4 invention issue, again, it's not a defense, and at this
5 point, he's already said that there was an invention,
6 and the jury should be instructed that there is no prior
7 invention defense, that Abbott is not claiming here it
8 was the first to invent.

9 MR. LEE: Your Honor, you've already
10 ruled that the patent, the Salfeld patent, is in, and
11 that's all I asked.

12 THE COURT: I don't think he's gone too
13 far. I think he was about to drop off into something
14 that I was going to have to instruct the jury. So I'm
15 not going to give them any further -- your request is
16 denied.

17 Now, Mr. Lee, stay away from that. Don't
18 you be going in --

19 MR. LEE: Yeah.

20 THE COURT: You do not want me talking to
21 that jury.

22 MR. LEE: I agree.

23 THE COURT: Okay. You know that better
24 than I do.

25 MR. LEE: I do. I got it.

1 THE COURT: And if I can give you some
2 names of references to lawyers that have had that
3 experience, then you don't want them, because I don't
4 talk very nicely.

5 MS. MULLIN: The third one was actually
6 the subject of a motion in limine. We had initially
7 proposed a motion in limine to preclude Dr. Marks from
8 testifying that enablement required enablement of a
9 therapeutic antibody.

10 And we were advised that you agreed to
11 that motion in limine, and so we didn't actually proceed
12 with -- with it. But we can show you the e-mail saying
13 that you agreed that he would not do that, and he's up
14 on the stand, and he just said you have to -- you
15 couldn't get an antibody with therapeutic properties,
16 so --

17 MS. ELDERKIN: He said you could not use
18 B-cells to get a human antibody that would be licensed
19 by the FDA.

20 MS. MULLIN: That would have therapeutic
21 properties.

22 MR. LEE: Well, I'll -- I've been very
23 careful trying to say fully human, high affinity,
24 neutralizing, so --

25 THE COURT: I don't remember ruling on

1 that, but --

2 MS. MULLIN: That's because they agreed
3 to it.

4 THE COURT: Well, if you agreed to it,
5 then it's in the order. I mean, we put -- all those
6 matters that were represented to as agreed to became
7 part of the motion in limine.

8 So you need to look at that paragraph,
9 and if you need further -- if y'all can't agree as to
10 how you're going to clear it up, then I'll clear it up.

11 MR. LEE: Okay.

12 MS. ELDERKIN: Can I raise one other
13 thing, Your Honor, since we're talking about the Salfeld
14 patent being prior art.

15 Dr. Marks' testimony in his report is,
16 well, the Salfeld patent anticipates if Humira infringes
17 the patent.

18 THE COURT: I cleared -- I said
19 yesterday, if has not -- is not occurring in this case.

20 MS. ELDERKIN: And his testimony is that
21 it does not infringe, and he's going to -- about to say
22 that it is anticipated.

23 MR. LEE: No. I covered that, and I
24 moved on. But we've got the patent in evidence, Your
25 Honor.

1 MS. MULLIN: So just to be clear on the
2 record, he's not going to give an opinion that the '775
3 patent is anticipated by the Salfeld '382 patent?

4 MR. LEE: He doesn't need to do that,
5 because the patent specifically covered the D2E7. You
6 claim D2E7 infringes.

7 MS. MULLIN: I just want to make sure
8 that he's not going to give any evidence.

9 MR. LEE: Well, I can -- if that's
10 correct, then it's invalid. But we're all focusing on
11 February 1994, so that's what we're focused on.

12 THE COURT: Well, okay. Let me make this
13 clear. In the written filing that the Defendant made
14 with this Court concerning this issue of judicial
15 estoppel and I raised before we started this trial, what
16 you said was, you were proposing to offer an alternative
17 opinion that was consistent with what their opinion had
18 been prior to me granting your Motion for Summary
19 Judgment. That's what your pleadings said.

20 MR. LEE: That's correct.

21 THE COURT: Okay. I'm expressly telling
22 you now on the record, which I think I've previously --
23 that there are not going to be no alternative opinions.

24 MR. LEE: Your Honor, we understand that
25 clearly, and we're not going to ask him about the '92

1 application, because we understand that's off limits.
2 This was about the 2002 application and the Salfeld 2000
3 patent, which you did rule on in the limine as coming in
4 because it is prior art, and that's it.

5 MS. MULLIN: The issue is not, is the
6 patent itself in evidence; the issue is, is this witness
7 able to provide testimony that it anticipates the '775
8 patent when that is not in his report?

9 MR. LEE: You know, respectfully, Your
10 Honor, this can all be cleared up if they just told us
11 what priority date they're relying upon.

12 THE COURT: Well, I told you now what the
13 priority date is.

14 MR. LEE: I understand.

15 THE COURT: I understand that all of this
16 could have been cleared up, but that's not where we are.
17 We're not playing what if, okay?

18 MR. LEE: Right. So it's '94, right?

19 THE COURT: Well, it's '94, I have
20 established. It's not any earlier than '94.

21 MR. LEE: '94. Okay.

22 THE COURT: Okay. I've established that.
23 But I'm instructing -- I've instructed all of you, don't
24 start trying to offer any opinions that are not in the
25 reports.

1 MR. LEE: Right.

2 THE COURT: With respect to your expert,
3 your rebuttal expert, he says that it was enabled in the
4 '92 application, and the testimony is, well, for the
5 same reasons, it was enabled by the '94 application.
6 Since I've got you up here, what -- you can take the
7 reasons in the '94 application that he identified that
8 were in the '92 application but no testimony about the
9 '92 application enabled it. But you can identify the
10 common matters that were in the '92 that were carried
11 forward in the '94.

12 MR. LEE: Right.

13 THE COURT: I'm going to allow you to do
14 that based upon the fact that it would be unfair in
15 light of the fact that I have granted summary judgment
16 right before trial.

17 MR. LEE: Yeah. And so I can clarify,
18 Your Honor, Dr. Marks' -- in Dr. Adams' report, he did
19 do -- you know, he did reference those. He did not
20 discuss any of the additional parts of the '94
21 application that Dr. Ghrayeb referred to, and we assume
22 those are off ground -- limits because they're not in
23 his report.

24 THE COURT: They're not going to be able
25 to ask him to consider those additional matters.

1 MR. LEE: Right. And he never gave an
2 opinion on the '94 application.

3 THE COURT: Well, he gave an opinion that
4 it was enabled for the same -- for the same reason he
5 said the '92.

6 MR. LEE: Right.

7 THE COURT: Okay. And y'all had him
8 identify the specific matters in the '92 application.

9 MR. LEE: Right.

10 THE COURT: Okay. What I am saying that
11 to the extent those were carried -- they were all
12 carried forward into the '94 application.

13 MR. LEE: Right.

14 THE COURT: I'm going to allow him to say
15 that the '94 application was enabled for those
16 identified reasons --

17 MR. LEE: Okay.

18 THE COURT: -- without reference to the
19 '92 application.

20 MS. MULLIN: Thank you, Your Honor --

21 THE COURT: Those are the things that are
22 carried forward.

23 MS. MULLIN: -- for the clarification.

24 THE COURT: Those are the -- remember,
25 those were the matters that were carried forward. That

1 was not in his report, I agree with that.

2 MR. LEE: Right.

3 THE COURT: But you were placed on fair
4 notice that that's what they were claiming, and it would
5 be materially unfair, given the state -- you got the
6 very benefit of my ruling, and that's -- of my summary
7 judgment ruling, and that's as far as we're going,
8 Mr. Lee.

9 MR. LEE: Okay.

10 THE COURT: But I'm telling you, if you
11 go further, with the amount of time I've spent
12 instructing this jury, it will be unfortunate for your
13 client in front of this jury, because I will start
14 telling them what you're doing, that you're violating my
15 specific instructions. You don't want to do that.

16 MR. LEE: Yeah. I haven't gotten close
17 to the '92 application yet.

18 THE COURT: Well, I know it, but you seem
19 to not want --

20 MR. LEE: No. I --

21 THE COURT: I know you don't agree with
22 me. You don't have to agree with me.

23 MR. LEE: Yeah. I --

24 THE COURT: You just got to follow my
25 instructions. That's my job.

1 MR. LEE: And the truth of the matter is
2 I went back and reread the side-bar yesterday, and I was
3 confused.

4 THE COURT: Okay.

5 MR. LEE: And we were going to ask you
6 before Dr. Adams. But we now understand what the ground
7 rules are. I think the issue has been briefed by both
8 of us. Your Honor has ruled what's in, and, you know --

9 THE COURT: And if I'm wrong, you're
10 going to get a chance to tell those three judges, and I
11 will respect their opinion as much as anybody --

12 MR. LEE: Yeah.

13 THE COURT: -- so -- if I'm wrong.

14 MR. LEE: And all I'm doing is
15 respectfully disagreeing, but I'm not going to get close
16 to it.

17 THE COURT: Well, I don't mind you
18 disagreeing, you know, and I appreciate you respectfully
19 disagree, but what starts -- what happens in front of
20 this jury, contrary to my instructions, then as a young
21 judge from Chicago cornered me and said, Don't you think
22 it's our job to run a tight ship, and I told her
23 absolutely.

24 You know, and if they say you run a tight
25 ship, that's a compliment to me. And if I run too tight

1 a ship, I'm sorry.

2 MR. LEE: We got it.

3 THE COURT: Okay.

4 MS. MULLIN: Thank you, Your Honor.

5 MS. ELDERKIN: Thank you, Your Honor.

6 (Recess.)

7 COURT SECURITY OFFICER: All rise.

8 (Jury in.)

9 THE COURT: Please be seated.

10 Ladies and Gentlemen, I want to clear up
11 one little matter for you.

12 With respect to this question on
13 enablement, which the witness has been testing about --
14 testifying about, I want you to know that enablement
15 does not require in a manner to meet the lofty standards
16 for success in the commercial marketplace, that is, in
17 the case of a drug, which we're talking about here, and
18 treatment, it's not required that it be commercially
19 viable or have any particular therapeutic use.

20 To the extent that either directly or
21 indirectly Dr. Marks' testimony has suggested such,
22 that's incorrect, and you should disregard that part of
23 the testimony.

24 Thank you. Let's proceed.

25 MR. LEE: Thank you, Your Honor.

1 Q. (By Mr. Lee) Dr. Marks, just to be clear, is
2 it your understanding that for the product to be
3 enabled, you must have a therapeutic product?

4 A. No, you do not need to.

5 Q. And there was some mention of FDA approval or
6 licensing.

7 Does the FDA approve products or license
8 products?

9 A. The FDA approves products.

10 Q. Are you familiar with something called the
11 Wands factors?

12 A. Yes, I am.

13 Q. What are the -- that's a legal concept?

14 A. Yes, it is.

15 Q. And what are the Wands factors?

16 A. The Wands factors are eight criteria that can
17 be applied to the claims, the specs in a patent, to
18 determine whether the patent is or is not enabled.

19 Q. And did you consider the Wands factors in
20 forming your opinion on infringement?

21 A. Yes, I did.

22 MR. LEE: Could we have Demonstrative 36,
23 please?

24 Q. (By Mr. Lee) Can you tell the jury what's on
25 the screen?

1 A. Right. So these are the eight Wands factors
2 and they are grouped in pairs so that there are only
3 four numbers.

4 Q. Now, let's take the first. What is the first?

5 A. The first is the nature of the invention and
6 the breadth of the claims.

7 Q. And did you consider the nature of the
8 invention and the breadth of the claims?

9 A. Yes, I did.

10 Q. And did you consider whether the claims covers
11 human and humanized antibodies?

12 A. Yes, I did.

13 Q. Now, let's focus on the second category.
14 What's the second category?

15 A. The second category is whether there are any
16 working examples and the amount of direction or guidance
17 disclosed in the patents.

18 Q. And how did those factors affect your opinion?

19 A. They supported or confirmed my opinion that
20 the patent was not enabled.

21 Q. Now, you're familiar with the concept of
22 example as it's use in the patent specification?

23 A. Yes, I am.

24 Q. And what is an example as it's used in the
25 patent specification?

1 A. An example shows or teaches how to make human
2 antibodies or how to use human antibodies or how -- or
3 characterization of human antibodies.

4 Q. Now, focusing on the 1994 application, do --
5 what do the examples in the patent application address?

6 A. They all address chimeric antibodies.

7 There's -- there is nothing in the example
8 that teaches how to make, how to test, or how to use
9 human antibodies.

10 Q. Now, are there any examples that describe
11 making a fully human antibody?

12 A. There are not.

13 Q. Let's go to the third set of Wands factors.

14 MR. LEE: Can we have those back on the
15 screen?

16 Q. (By Mr. Lee) What are -- what is the third
17 set?

18 A. State of the art and its predictability.

19 Q. And would you tell the jury how did that
20 affect your opinion concerning life in the field in
21 1994?

22 A. Yes. So -- so by applying these, also
23 confirmed my opinion that the patent was not enabled.
24 The state of the art, meaning the ability and the tools
25 to make human antibodies at that time -- as I said, it

1 was very, very early days. And in terms of the skill in
2 the art, there were a few people who were very skilled
3 or learning how to be skilled in making human
4 antibodies, but that knowledge was very limited.

5 So when I looked at the patent, I would have
6 expected, if it were enabled, for there to be
7 significant teaching on how to make what at that time
8 was extremely challenging to make in general, human
9 antibodies, and I found no teaching at all.

10 MR. LEE: Let's bring up DDX35.

11 Q. (By Mr. Lee) Again, I want to focus you on
12 this February 1994 time period. Let's take the three
13 different methods in order.

14 In February 1994, could the technique of human
15 B-cell technology be used to make high-affinity,
16 neutralizing antibodies, anti-TNF-alpha antibodies?

17 A. No.

18 Q. In fact, I think you told us before, it has
19 never been done, correct?

20 A. That's correct. Not -- not that I'm aware of.

21 Q. Let's look at phage display. And, again, you
22 have the date, February of 1994 in mind?

23 A. Yes, I do.

24 Q. Could phage display be used to make
25 high-affinity, neutralizing antibodies to TNF without

1 undue experimentation in 1994?

2 A. No, not without undue experimentation.

3 Q. All right. Could you yourself, having been
4 working in the field, have made a high-affinity,
5 neutralizing antibody to TNF-alpha without undue
6 experimentation?

7 A. In 1994, not without undue experimentation.

8 Q. And why not?

9 A. Because at that time the technologies that we
10 had invented or had at our hands were these very small
11 libraries. And from those very small libraries, we got
12 very few antibodies. So there were few antibodies to
13 test, and they were very low-affinity.

14 And at that time, we did not know how to make
15 the libraries bigger, which we ultimately learned in
16 order to get more antibodies and better antibodies. And
17 we also did not know at that time how to turn those very
18 low-affinity antibodies into high-affinity antibodies
19 that would meet the scope of the claims.

20 Q. Let's go to the third technique. Again,
21 focusing on February 1994. Can you do that?

22 A. Yes, I can.

23 Q. Could the technique of transgenic mouse --
24 mice be used to make high-affinity, neutralizing
25 antibodies to TNF without undue experimentation?

1 A. No.

2 Q. And why not?

3 A. So this was also very early days for the
4 transgenic mice technology. In fact, the mice didn't
5 have all the antibody genes that humans had.

6 In addition, they were not quite as healthy as
7 normal mice, and for reasons that were really unclear,
8 they didn't remount as vigorous an immune response as
9 non-transgenic mice would have mounted.

10 Q. Let's go back to the Wands factors, which is
11 DDX36.

12 A. Yes.

13 Q. Did you consider the relative skill of the art
14 and quantity of experimentation necessary to produce a
15 fully human antibody?

16 A. Yes, I did.

17 Q. How did those affect your opinion on
18 enablement?

19 A. They confirmed my opinion that the patent was
20 not enabled.

21 Q. Why is that?

22 A. Because as I have mentioned there, that while
23 there were skilled antibody engineers around at that
24 time, there were very few individuals who were actually
25 skilled in using these technologies to make human

1 antibodies.

2 And I would have expected, again, to see in
3 the patent, therefore, a significant teaching on how to
4 make and use human antibodies. And I saw none.

5 Q. Now, in 1994, how many scientists were working
6 in the antibody engineering field?

7 A. In the antibody engineering field, many
8 scientists -- I don't really know quite how many. When
9 you went to scientific meetings at that time on antibody
10 engineering, there would be a few hundred scientists.

11 Q. Now, in forming your opinions concerning
12 enablement in 1994, did you consider efforts by the
13 parties in this case to make human antibodies?

14 A. Yes, I did.

15 Q. And what efforts did you consider?

16 A. I considered the failed efforts by Casali and
17 the failed testing by Le. And I also considered the
18 efforts by BASF science testing, including Dr. Salfeld
19 and his collaborators at Cambridge Antibody Technology.

20 Q. And those are efforts that you've described to
21 us earlier?

22 A. That's correct.

23 Q. In forming your opinion on enablement, did you
24 consider the amount of experimentation that was required
25 for Abbott's efforts that culminated with Humira?

1 A. Yes, I did.

2 Q. And how did that affect your opinion?

3 A. It -- it confirmed my opinion that the patent
4 was not enabled.

5 Q. Because?

6 A. So when I considered that effort, I realized
7 that the individuals who were doing that work were,
8 first of all, not of ordinary skill in the art. They
9 were experts in the art. And I know that because
10 Cambridge Antibody Technology was located just down the
11 road from Dr. Winter's laboratory in Cambridge.

12 In fact, Dr. Winter was one of the founders of
13 Cambridge Antibody Technology. And two of the people
14 who worked at Cambridge Antibody Technology, I worked
15 with in Dr. Winter's lab, Dr. McCafferty and
16 Dr. Hoogenboom, and they were certainly experts in the
17 art.

18 So, first of all, the work at Cambridge
19 Antibody Technology was done by experts in the art, not
20 those of ordinary skill in the art.

21 They also used the type of antibody libraries,
22 probably better antibody libraries than we had described
23 in the early 1990s, including in my 1993 publication.
24 And what we know is that when using those libraries,
25 that effort failed.

1 And in order for that effort to succeed, the
2 scientists at CAT and BASF had to invent new technology
3 called guided selection, for which they received a
4 patent. But even that was not enough.

5 And then had they required significant
6 additional experimentation, a year plus of very hard
7 work, inventing technologies to make those low-affinity
8 antibodies bind tighter and also how to find those very
9 tightly binding needles, the antibodies, the needles in
10 the haystack, in the fields of haystacks, so...

11 Q. Now, have you given us the bases for your
12 opinion that the -- that the 1994 application did not
13 teach someone how to make and use what's described in
14 Claims 2, 3, 14, and 15?

15 A. That's correct.

16 Q. Now, let's go to the written description
17 requirement.

18 Again, this is another legal requirement?

19 A. Yes, it is.

20 Q. And His Honor will instruct the jury on its
21 meaning, but what's your understanding?

22 A. My understanding is the written description
23 requirement requires that the inventors show that
24 they -- show that they have the invention or how to use
25 the invention, that they have human antibodies and

1 show -- show how to use human antibodies.

2 Q. Now, the -- in his pre-instructions to the
3 jury before the case started, His Honor mentioned
4 disclosing to the jury the claimed invention.

5 Remember that?

6 A. Yes.

7 Q. And do you understand that to be, in part, the
8 written description requirement?

9 A. Yes.

10 Q. And is it a different requirement or the same,
11 as you understand it, for enablement?

12 A. It's a different requirement than from
13 enablement.

14 Q. So let's talk now about the written
15 description requirement.

16 Do the terms human antibodies or human
17 variable regions appear in some places in the 1994
18 applications?

19 A. The words appear.

20 Q. And do the words by themselves, in your
21 opinion, provide an adequate written description of the
22 invention?

23 A. No, they do not.

24 Q. And do the inventor's effort tell you that
25 they have made a fully human antibody?

1 A. No.

2 Q. Do they tell you how to do it?

3 A. No, they do not.

4 Q. Do they tell you they had possession of it?

5 A. No, they do not.

6 Q. Now -- and have you reviewed all of the
7 applications from the beginning leading up to February
8 of 1994?

9 A. Yes, I have.

10 MR. LEE: Now, let me bring up the '775
11 patent. Can we do that?

12 And could I have the first column?

13 And could we enlarge the first paragraph
14 in the first column?

15 Q. (By Mr. Lee) Do you see the last sentence,
16 which says: Each of the above applications are entirely
17 incorporated herein by reference?

18 A. Yes, I do.

19 Q. And have you considered these earlier
20 applications that are incorporated by reference?

21 A. Yes, I have.

22 MR. LEE: Can I have Defendants'
23 Exhibit 25 -- which is already in evidence, Your
24 Honor -- on the screen?

25 Q. (By Mr. Lee) What is Defendants' Exhibit 25?

1 MR. LEE: Maybe if we could go to the
2 second page.

3 A. Thank you.

4 It is an earlier application by Le, et al.

5 Q. (By Mr. Lee) All right. And this is one of
6 the applications that's incorporated by reference into
7 the '775 patent?

8 A. Yes, it is.

9 MR. LEE: Could we turn to Page 9?

10 And could we enlarge the full paragraph
11 in the middle?

12 Q. (By Mr. Lee) Do you see the paragraph that
13 begins: The development of human monoclonal antibodies
14 that could circumvent the above problems has encountered
15 a number of obstacles?

16 A. Yes, I do.

17 Q. And without going through each sentence, in
18 general terms, what is described by the inventors in the
19 remainder of this paragraph in the application?

20 A. It basically describes how hard it is to make
21 human antibodies.

22 Q. Now, were you present in the courtroom when I
23 asked Dr. Ghrayeb about these different challenges in
24 making antibodies?

25 A. Yes.

1 Q. And were you present when I asked him if the
2 application discloses any solution to these problems?

3 A. Yes, I was.

4 Q. Were you present when he said no?

5 A. Yes.

6 Q. Do you agree with Dr. Gering, do the -- does
7 the '775 patent specification describe solutions to
8 these problems?

9 A. No, it does not.

10 Q. And have you reviewed the full range of all
11 the applications leading up to the '775 patent?

12 A. Yes, I have.

13 Q. And do any of those applications provide a
14 solution to these problems?

15 A. No, they do not.

16 Q. Is there any sequence information in the '775
17 patent for the key region of the lock and key for fully
18 human antibody?

19 A. No, there is not.

20 Q. Now, when Dr. Gering testified, he --
21 Ms. Elderkin put him through some different sections of
22 the specification.

23 Do you remember that?

24 A. That's correct.

25 Q. And he asked you whether -- she (sic) was

1 asked what they described and how it related to human
2 antibodies.

3 A. Yes, I remember that.

4 Q. I want to take you quickly through each of
5 them.

6 Have you reviewed the portions that he
7 referred to?

8 A. Yes, I have.

9 Q. And they were all in the 1994 application?

10 A. That's correct.

11 Q. And I want to go through them quickly and ask
12 you whether they disclose to one of ordinary skill in
13 the art the inventors who were in possession of the
14 human antibody invention or taught someone how to do it.

15 MR. LEE: So let's bring up Column 5,
16 Lines 55 to 59 of the patent.

17 Q. (By Mr. Lee) And you refer to the anti-TNF
18 antibodies are intended to include at least one of the
19 monoclonal rodent/human chimeric antibodies, rodent
20 antibodies, human antibodies, or any portions thereof,
21 having at least one antigen-binding region, and then it
22 goes on.

23 Do you see that?

24 A. Yes, I do.

25 Q. Now, is this one of the places where the

1 February 1994 application mentions human antibodies?

2 A. Yes, it is.

3 Q. Other than mentioning the words, does it say
4 anything else?

5 A. No. The words appear, but there's no
6 indication -- there's no indication here that the
7 inventors have the antibodies. And there's no teaching
8 here on how to make human antibody.

9 MR. LEE: Let's go to Column 16, Line 26
10 to 57, which Dr. Ghrayeb testified about.

11 Q. (By Mr. Lee) Do you remember him testing --
12 testifying about this portion called recombinant
13 expression of anti-TNF antibodies?

14 A. Yes, I do.

15 Q. And does this passage teach one of ordinary
16 skill in the art how to make or use a human antibody to
17 TNF?

18 A. No, it does not.

19 Q. Why not?

20 A. There are -- there's no indication in there
21 that they have human antibodies. There's no specific
22 teaching on how to make human antibodies. These are
23 cloning techniques, very general cloning techniques.

24 Q. And if you follow these general cloning
25 techniques, could you get a fully human neutralizing,

1 high-affinity antibody?

2 A. No, you could not have.

3 MR. LEE: Let's turn to Column 18,
4 Line 29 to 67.

5 Q. (By Mr. Lee) Do you have that before you?

6 A. Yes, I do.

7 Q. Now, we're not going to go through it in
8 detail.

9 Dr. Ghrayeb also mentioned this. In general
10 terms, what does this portion of the patent describe --
11 patent application and specification describe?

12 A. Again, it describes very general library
13 technologies that could be used to make antibodies,
14 including human antibodies. But, in fact, the only
15 reference there to library technologies is reference to
16 my own paper. That would be the Marks 1993 publication.

17 Q. Now, does this portion teach anyone how to
18 make or use a fully human antibody?

19 A. No, it does not.

20 Q. Could you follow the techniques that are
21 described in this portion of the specification and make
22 one that fell within the scope of the claims?

23 A. No. You could not make one that fell within
24 the scope of the claims.

25 Q. Let's go to the next portion he referred the

1 jury to, which is Column 18, Line 48 to 53.

2 Do you have this portion in front of you?

3 A. Yes, I do.

4 Q. Again, what is being described here?

5 A. A library technique to make antibodies.

6 Q. And there is a specific reference to a paper

7 Dr. Ghrayeb mentioned called Marks, et al,

8 biotechnology, October 1993.

9 A. That's correct.

10 Q. And he discussed that paper with the jury and
11 talked about what it described, correct?

12 A. I believe so.

13 Q. Are you familiar with the paper?

14 A. Yes. I wrote that paper.

15 MR. LEE: Let's bring up DX381 --
16 preadmitted, Your Honor -- and put it on the screen.

17 Q. (By Mr. Lee) Is this the paper?

18 A. Yes, it is.

19 Q. And it was published when?

20 A. In October of 1993.

21 Q. And you are one of the authors, correct?

22 A. I am the first author.

23 Q. Does this publication teach one of ordinary

24 skill in the art how to make human antibodies to TNF

25 following the scope of the claims?

1 A. No, it does not.

2 Q. Would you explain why?

3 A. Yes. What this paper specifically does is
4 teach how to make low-affinity antibodies to red blood
5 cells. The techniques that were used in this paper were
6 the early phage antibody libraries that myself and
7 others in Greg Winter's lab invented.

8 The properties of those libraries were such
9 that the antibodies coming out of them were very
10 low-affinity and would not meet the scope of the claims.
11 They would have been probably poorer versions of the
12 libraries than Cambridge Antibody Technology used when
13 they worked with Abbott to attempt to make a TNF-alpha
14 antibody, and they failed.

15 So there's no teaching in this paper about how
16 to make TNF antibodies. In fact, there's no teaching in
17 this paper how to make phage antibody libraries. And
18 the library that is described in there would not have
19 been adequate to make TNF-alpha antibodies.

20 And one way we know that is -- that it was
21 used -- a library very similar to it, or perhaps even
22 that library, was used, and it did not succeed.

23 MR. LEE: Let's turn to Column 33, Line
24 19 to 23, which is another portion of the patent
25 specification that Dr. Ghrayeb referred to.

1 Q. (By Mr. Lee) Do you recall this?

2 A. Yes, I do.

3 Q. In very general terms, what is described at
4 this portion of the 1994 application and the
5 specification?

6 A. So what this -- what this describes is the use
7 of molecular modeling to try to increase the affinity of
8 antibodies. And so a molecular model is like a model.
9 I used to build, you know, airplane models when I was a
10 kid. So it's the same type of thing.

11 You make a model, but unlike a model of an
12 antibody, it doesn't -- there's not a little kit where
13 you glue everything together. And so the technologies
14 at the time were not very good at modeling. So we
15 didn't really know how to model an antibody. We didn't
16 know how to model TNF. We certainly didn't know how to
17 model how the antibody bound to TNF.

18 And one would not have been able to take the
19 knowledge at that time and use it to make a model of an
20 antibody interacting TNF and then be able to use that
21 model to increase the affinity of the antibody.

22 Q. Now, let's turn to Column 34, Line 26 through
23 33, which Dr. Ghrayeb also referred to.

24 Do you recall him testifying about this
25 portion of the specifications?

1 A. Yes, I do.

2 Q. And can you read it better on the screen, or
3 would you like it blown up?

4 A. Can you go up just a little bit higher so I'm
5 sure.

6 Yes, I do.

7 Q. And in general terms, what is described in
8 this portion of the application in the specification?

9 A. So this also describes the use of modeling to
10 increase antibody affinity. But for the same reasons I
11 have previously described, this approach, in 1994, would
12 not have worked.

13 Q. Let's turn to the last portion that he cited,
14 which is Column 36, Lines 3 to 12.

15 A. Yes.

16 Q. What is described there?

17 A. A way of administering an antibody drug.

18 Q. To a patient?

19 A. To a patient. Sorry.

20 Q. And does it tell you anything about whether
21 Centocor -- whether the inventors had disclosed or
22 taught how to make and use a fully human antibody?

23 A. Not at all.

24 Q. So let's take the collection of all of the
25 different points that Dr. Ghrayeb relied upon and

1 everything else that's in the '94 application.

2 Do you have that in mind?

3 A. Yes, I do.

4 Q. And I want to focus you very specifically on
5 the February 1994 application.

6 A. Okay.

7 Q. And you've reviewed that carefully.

8 A. Yes, I have.

9 Q. Does that application describe to one of
10 ordinary skill in the art how to make a fully human
11 antibody falling within the scope of the claims?

12 A. No, it does not.

13 Q. Does it describe to one of ordinary skill in
14 the art how to use an antibody that falls within the
15 scope of the claims?

16 A. No, it does not.

17 Q. Does it describe how one of ordinary skill in
18 the art would use the techniques that are described in
19 general to make or use that antibody?

20 A. No, it does not.

21 Q. Does it describe whether the inventors
22 actually had made a fully human antibody falling within
23 the scope of the claims?

24 A. No, it does not.

25 Q. Now let's turn to the third part of your

1 opinion on validity which concerns anticipation.

2 A. Okay.

3 Q. Mr. Beck reminds me of one other question.

4 MR. LEE: Could I bring up Figures 16 and
5 16A and 16B.

6 I apologize. We're just going to go
7 back --

8 THE WITNESS: That's okay.

9 MR. LEE: And I had forgotten this.

10 Q. (By Mr. Lee) Dr. Ghrayeb had also referred to
11 Figure 16A and 16B, and he told us what they were,
12 correct?

13 A. That's correct.

14 Q. And these are, again, part of the '94
15 application?

16 A. Yes, they are.

17 Q. And what are Figures 16A and 16B?

18 A. These are the DNA and the protein sequences of
19 a mouse antibody.

20 Q. And how do the protein sequences of the mouse
21 antibody, or the chimeric antibody, compare to a full
22 human antibody?

23 A. They're very different.

24 Q. And would the disclosure of this sequence
25 information teach one of ordinary skill in the art how

1 to make and use a fully human body?

2 A. No.

3 Q. -- falling within the scope of the claims?

4 A. No.

5 Q. Now let's turn to anticipation. This is
6 another legal concept, correct?

7 A. That is correct.

8 Q. Which His Honor will instruct the jury,
9 correct?

10 A. That's my understanding.

11 Q. And as you understand it, what does
12 anticipation mean?

13 A. Anticipation means that in a single piece of
14 prior art, all of the elements of the claims are met.

15 Q. All right. Now, what do you understand prior
16 art to mean?

17 A. Prior art would be a prior publication; it
18 could be a paper; it could be a patent.

19 Q. Now, as a scientist -- it's work done before
20 February of 1994?

21 A. That's correct.

22 Q. Now, as a scientist, how did you analyze
23 Claims 2, 3, 14, and 15 to see if they were anticipated?

24 A. I -- I placed all of the elements of the
25 claims up against a single piece of prior art, and then

1 I went through each element one by one to see if they
2 were contained within the piece of prior art.

3 Q. Now, is there a particular piece of prior art
4 that you've relied upon?

5 A. Yes, there is.

6 Q. And what is that particular piece of prior
7 art?

8 A. It's an Adair 1992 publication.

9 MR. LEE: And can we bring up DX361?
10 Which is in evidence, Your Honor.

11 Q. (By Mr. Lee) Do you have that before you?

12 A. Yes, I do.

13 Q. Would you explain to the Ladies and Gentlemen
14 of the jury what DX361 is?

15 A. Yes. DX -- this demonstrative is a patent
16 that was published in July -- on July 9th, 1992 by Adair
17 and other inventors.

18 Q. Now, you referred to it as a demonstrative.
19 Is this a demonstrative, or is this the actual --

20 A. It's a patent.

21 Q. -- patent?

22 Now, it was published in July of 1992?

23 A. That's correct.

24 Q. All right. And have you reviewed it and
25 reviewed it closely?

1 A. Yes, I have.

2 Q. Now, first, in general terms, what do
3 Dr. Adair and his colleagues describe in this
4 publication?

5 A. High-affinity, neutralizing humanized
6 antibodies to TNF-alpha.

7 Q. And if you think back to the four categories
8 of antibodies we described for the jury: A mouse,
9 chimeric, humanized, human, which of that category?

10 A. So it's the third type of antibody. It's the
11 humanized antibody, or just the very tips that touch TNF
12 or a mouse.

13 Q. And did Dr. Ghrayeb give the antibody a
14 specific number or a name?

15 A. Yes. He called it CDP571.

16 Q. Can you and I refer to it as the Adair
17 antibody just for the purposes of today?

18 A. Yes, we can.

19 Q. Now, have you compared the Adair 1992 patent
20 to the claims that Centocor's asserting in this case?

21 A. Yes, I have.

22 Q. Now, did Adair disclose human and humanized?

23 A. No. It only discloses humanized.

24 Q. And to anticipate a claim, Claim 2, Claim 3,
25 Claims 14 and 15, what is your understanding; do you

1 have to have both or either?

2 A. Either one will do it, human or humanized.

3 Q. All right. Now, are there examples in the
4 1992 Adair patent?

5 A. Yes, there are.

6 Q. And examples, as you've used the term examples
7 before, correct?

8 A. That's correct.

9 Q. And what do those examples disclose?

10 A. They disclose how to make and how to test
11 high-affinity, neutralizing humanized antibodies to TNF.

12 Q. So there are specific examples showing that
13 someone has made and tested a humanized antibody?

14 A. That's correct.

15 Q. Now, have you compared the Adair publication
16 to the elements in Claims 2, 3, 14, and 15 of the '775
17 patent?

18 A. Yes, I have.

19 Q. What did you conclude?

20 A. I concluded that the Adair 1992 publication
21 anticipates each and every element of the claims.

22 Q. Would a demonstrative exhibit assist you in
23 explaining that to the jury?

24 A. Yes, it would.

25 MR. LEE: Could we have DDX47, which is

1 the '775 patent?

2 Q. (By Mr. Lee) What is shown here?

3 A. Those are the claims, Claims 1, 2, 3 and 13 to
4 15.

5 Q. All right. And just so we can deal with just
6 one of the claims, what's the difference between -- or a
7 couple of the claims -- what's the difference between
8 Claims 1 and 2 on the one hand and 14 to 15 on the
9 other?

10 A. Yes. So the differences are that Claims 13,
11 14, and 15 require a specific type of human, what's
12 called IgG, or a type of antibody. And that would be an
13 IgG1 antibody.

14 So Claims 1, 2, 3 cover a general IgG
15 antibody. And Claims 13, 14, and 15 describe a specific
16 type of IgG, the IgG1.

17 Q. Now, let's walk through the claim elements.

18 MR. LEE: And could I have Demonstrative
19 Exhibit 45 on the screen?

20 Q. (By Mr. Lee) Now, you remember when Dr. Adams
21 was doing the -- his infringement analysis, he had a
22 claim chart up here like this?

23 A. Yes, I do.

24 Q. And he put on the left-hand side the elements
25 of the claim?

1 A. Yes.

2 Q. And on the right-hand side where in Humira he
3 found each of the elements?

4 A. That's correct.

5 Q. Now, do you recall there's one element that
6 requires competitive inhibition, which is the second
7 paragraph here.

8 Do you see that?

9 A. Yes, I do.

10 Q. And he said that all of the other elements,
11 other than competitive inhibition, were found in Humira,
12 and Abbott admitted as much, correct?

13 A. That's correct.

14 Q. Let's just focus on all those other elements.

15 Does the Adair 1992 publication, in 1992, have
16 all of those other elements?

17 A. Yes, it does.

18 Q. So starting at the top where it refers to an
19 isolated recombinant anti-TNF-alpha antibody, does Adair
20 disclose that?

21 A. Yes.

22 Q. And how so?

23 A. It describes an isolated anti-TNF antibody
24 that has been cloned, and that antibody contains a human
25 constant region.

1 Q. All right. Now, I'm going to skip the
2 competitive inhibition limitation, as Dr. Adams did, but
3 we'll come back to it just as he did. And let's go to
4 the next, the third box, which begins binding to a
5 neutralizing epitope, and then goes on.

6 Do you see that?

7 A. Yes, I do.

8 Q. And do you find that in the Adair 1992
9 publication?

10 A. Yes. Adair measured the affinity of the Adair
11 antibody, and it was much higher or much better than the
12 number listed there.

13 Q. So it fell within the scope of the claims?

14 A. That's correct.

15 Q. Now, let's go to Claim 2, which adds some
16 additional requirements of a human constant region and a
17 human variable region.

18 Have you seen that?

19 A. Yes, I do.

20 Q. Does Adair disclose that?

21 A. Yes, it does.

22 Q. And would you explain to us how and where?

23 A. Because it -- it discloses the sequences of a
24 number of humanized antibodies to TNF, including what we
25 are calling the Adair antibody. And a humanized

1 antibody is derived from human DNA and meets the
2 definition of a human variable region.

3 Q. Now, let's go back to the second box from the
4 top, the competitive inhibition.

5 Does the Adair publication refer to
6 competitive inhibition with A2?

7 A. No, it does not.

8 Q. Can you conclude whether CDP571, the Adair
9 antibody, actually satisfies that limitation?

10 A. Yes, you can. Whether CDP571 competes or does
11 not compete with A2 would be an intrinsic property of
12 that antibody; in other words, it would be contained
13 within that antibody.

14 Q. Have you concluded whether the Adair antibody
15 competitively inhibits the bonding of A2?

16 A. Yes, I have.

17 Q. Now, Dr. Marks, on this issue of invalidity,
18 or anticipation, you understand that Abbott bears the
19 burden of proof?

20 A. Yes, I do.

21 Q. How did you determine whether this competitive
22 inhibition requirement was satisfied?

23 A. I relied on testing done in an independent
24 laboratory.

25 Q. And what was that laboratory?

1 A. Veritas.

2 Q. Did you review the testing protocols and the
3 results after the tests were done?

4 A. Yes, I did.

5 Q. And Veritas is a completely independent
6 laboratory, correct?

7 A. Yes, it is.

8 Q. And it was asked to do testing of CDP571?

9 A. Yes, it was.

10 Q. And were those tests the type of tests that
11 you would rely upon in the ordinary course of your work?

12 A. Yes, they are.

13 Q. And what did you conclude from having reviewed
14 the Veritas test?

15 A. I concluded that CDP571 competes with A2 for
16 binding to human TNF-alpha.

17 Q. And so Veritas, as you understand it, actually
18 did testing of CDP571 itself?

19 A. Yes, they did.

20 Q. Now, did Veritas do -- did you review a couple
21 of different tests of Veritas?

22 A. Yes, I did.

23 Q. And did you rely upon the collection of tests?

24 A. Yes, I did.

25 Q. And what did the collection of tests show you

1 about whether CDP571, or the Adair antibody, competes
2 with A2 as His Honor has described -- defined the
3 requirement?

4 A. They show that CDP571, or the Adair antibody,
5 competes with A2.

6 Q. Now, on this issue, as you said, Abbott bears
7 the burden of proof, correct?

8 A. That's correct.

9 Q. Veritas did testing, correct?

10 A. That's correct.

11 Q. Did Dr. Adams do any testing?

12 A. No, Dr. Adams didn't do any testing.

13 Q. Now, let's look at Claims 14 and 15, if we
14 could.

15 MR. LEE: And let's bring them up, maybe
16 DDX46 again.

17 A. Yes.

18 Q. (By Mr. Lee) And what is shown on this chart?

19 A. Claims 13 through 15 and then the parts of the
20 Adair reference that would relate to containing those
21 elements.

22 Q. Now, again, let me set aside the competitive
23 inhibition part of Claims 13, 14, and 15.

24 Can you do that?

25 A. Yes.

1 Q. And Centocor made the point that Abbott had
2 admitted that Abbott's Humira had all of these other
3 aspects of Claims 13, 14, and 15.

4 A. Correct.

5 Q. Did the prior art -- withdrawn.

6 Did the Adair reference in 1992 actually have
7 all of these elements as well?

8 A. Yes, it did.

9 Q. And did the Adair 1992 also have competitive
10 inhibition?

11 A. No, it did not.

12 Q. Did it have competitive inhibition with A2 as
13 required by the claims?

14 A. No, it did not.

15 Q. Well, let's go back to Claim 3.

16 A. Yes.

17 Q. All right. And I was -- I'm reminded by
18 Mr. Beck that I hadn't asked about Claim 3. And I'll
19 come back to 14 and 15 and finish.

20 Did you reach a conclusion as to whether the
21 Adair patent describes the additional elements of
22 Claim 3?

23 A. Yes, I did.

24 Q. So to close off Claims 2 and 3, before going
25 back to 14 and 15 -- and I apologize for that -- did you

1 reach a conclusion as to whether the Adair reference
2 discloses each and every element of Claims 2 and 3?

3 A. Yes, I did.

4 Q. And to go to this enablement issue that we've
5 talked about, did the Adair publication, in your view,
6 teach one of ordinary skill in the art how to make and
7 use the humanized antibody that it was describing?

8 A. Yes, it did.

9 Q. And how did it do that?

10 A. It shows the specific sequences of the
11 humanized antibodies.

12 Q. All right. Now, let's go back to Claims 14
13 and 15, which come off of Claim 13, correct?

14 A. That's correct.

15 Q. And we've discussed everything, other than
16 competitive inhibition, correct?

17 A. I believe so.

18 Q. And you just told me that competitive
19 inhibition is not expressly described in Adair, correct?

20 A. That's correct.

21 Q. There's no mention of A2 specifically,
22 correct?

23 A. No, there is not.

24 Q. But have you been able to reach a conclusion
25 as to whether that element is satisfied?

1 A. Yes, I have.

2 Q. And how did you do that?

3 A. I relied on testing done in an independent
4 laboratory.

5 Q. What laboratory?

6 A. Veritas.

7 Q. Is that the laboratory you described to us
8 earlier?

9 A. Yes, it is.

10 Q. And it's the kind of testing that you would
11 normally rely upon?

12 A. Yes, it is.

13 Q. And what did it show you?

14 A. It showed me that CDP571, or the Adair
15 antibody, competes with A2 for binding to TNF-alpha.

16 Q. Now, let me turn to the issue of infringement.
17 And you were present for Dr. Adams' testimony, correct?

18 A. That's correct.

19 MR. LEE: And if I could have Claims --
20 DDX47 back on the screen again.

21 Q. (By Mr. Lee) These are the claims again that
22 the jury is going to be asked to address, correct?

23 A. That's correct.

24 Q. And one of the points that Dr. Adams made was
25 that the dispute between Abbott and Centocor concerns

1 competitive inhibition, correct?

2 A. That's correct.

3 Q. So the dispute for the prior art and for
4 infringement is on the same limitation, competitive
5 inhibition?

6 A. That's correct.

7 Q. Now, do you understand that His Honor has
8 provided some guidance as to how this claim term should
9 be interpreted?

10 A. Yes, I do.

11 MR. LEE: Could we have DDX38?

12 Q. (By Mr. Lee) And can you tell us what's on the
13 screen in DDX38?

14 A. The Court's definition of competitively
15 inhibits binding of A2.

16 Q. And in considering the issue of infringement
17 and whether Centocor has borne its burden of proof, did
18 you consider -- I'm sorry -- withdrawn.

19 In considering the issue of infringement and
20 considering specifically the competitive inhibition
21 requirement, did you apply the definition that the Court
22 provided?

23 A. Yes, I did.

24 Q. Now, Centocor has the burden of proof on this
25 issue, correct?

1 A. That's correct.

2 Q. And Centocor did testing on this issue,
3 correct?

4 A. That's correct.

5 Q. Did you perform testing on this issue?

6 A. No, I did not.

7 Q. Did you evaluate Centocor's testing?

8 A. Yes, I did.

9 Q. Just as Dr. Adams evaluated Veritas' testing
10 on the issue of invalidity, correct?

11 A. Correct.

12 Q. Now, let's focus on this issue of competitive
13 inhibition.

14 Have you considered the two categories of
15 tests that Dr. Adams described?

16 A. Yes, I have.

17 Q. First, there was the testing of Humira by
18 Dr. Tam, correct?

19 A. That's correct.

20 Q. And have you reached a conclusion as to
21 whether that testing demonstrates that Humira satisfies
22 the competitive inhibition requirement?

23 A. Yes, I have.

24 Q. What is your conclusion?

25 A. My conclusion is that it does not.

1 Q. And why is it that it does not?

2 A. Because that test was done in the wrong
3 direction.

4 Q. What do you mean by done in the wrong
5 direction?

6 A. So that test shows that A2 competes with
7 Humira, but that test does not show that Humira competes
8 with A2.

9 Q. Now, there was some discussion during the
10 cross-examination of Dr. Adams about doing the test in
11 both directions.

12 A. I recall that.

13 Q. Would you explain to us, what does it mean to
14 do a competitive inhibition test in both directions?

15 A. So -- so briefly, it means that one would test
16 to see if Humira competes with A2 and to do a separate
17 set of tests to determine if A2 competes with Humira.

18 Q. And why does testing -- the direction of the
19 testing matter?

20 A. The direction matters, because there are
21 instances where a test that shows competition in one
22 direction will not show competition in another
23 direction.

24 Q. And have you helped prepare a demonstrative
25 that will illustrate this concept to the jury?

1 A. Yes, I have.

2 MR. LEE: Could we have DDX48 up, please?

3 And this is a very brief animation, Your Honor, so it
4 will move a little bit.

5 Q. (By Mr. Beck) Can you use this animation and
6 describe to the jury why it matters?

7 A. I can. Is there a laser pointer? This is the
8 one instance where I might be able to use it to point to
9 the screen.

10 MR. LEE: We have one.

11 If you could have just a second, Your
12 Honor.

13 Q. (By Mr. Lee) While Mr. Beck gets that, I'm
14 just reminded again by my colleagues that I didn't ask
15 you this question.

16 Do you have -- I asked you whether you had an
17 opinion -- I asked you whether you had an opinion as to
18 whether the Adair publication met all the elements of
19 Claim 3, but I'm reminded I didn't ask you what your
20 opinion was.

21 What is your opinion?

22 A. It does.

23 Q. Okay. Now, using the laser pointer, let's go
24 back to the idea of testing in two different directions.

25 Using DDX48, would you describe to the jury

1 why the direction of competition matters?

2 A. Right. So what we're going to look at in this
3 animation is to determine whether the yellow antibody
4 competes with the blue antibody for binding to TNF.
5 And the yellow antibody is going to want to bind right
6 there (indicates). That's where its binding site is.
7 And the blue antibody is going to want to bind right
8 there (indicates). That's where its binding site is.

9 Now, when we do these tests, we need to be
10 able to measure the binding of the blue antibody in
11 order to determine if there is competition. So we put a
12 label, which is this little yellow circle here, on the
13 blue antibody.

14 And as you heard from others, that label could
15 be radioactivity, or it could be something else we could
16 measure in the laboratory.

17 So now let's put this animation in play, and
18 what we see is the yellow antibody, when it binds to its
19 binding site here, prevents the blue antibody from
20 getting to its binding site.

21 And because the blue antibody doesn't get to
22 its binding site, there is no label attached to the TNF.
23 And so it wouldn't measure any binding of the blue
24 antibody, and we would say, then, that the orange
25 antibody competes with the blue antibody.

1 And we actually have a name for this type of
2 competition that occurs when the antibodies don't bind
3 to the same place but still one antibody competes with
4 another. And that name that scientists use is another
5 big name, and it's called steric hindrance, which is
6 just a fancy way of saying the antibody is getting in
7 the way of the other antibody.

8 Q. Can you give us an analogy, a real-world
9 analogy, that might describe the same concept of steric
10 hindrance?

11 A. Yes. If you have the pleasure of flying on
12 airplanes these days, which are always very crowded, and
13 you're trying to get to the window seat, if you go in
14 first, you can get to the window seat and then the
15 passenger who has the aisle seat can get in.

16 But if the passenger in the aisle seat gets in
17 first, you're going to have a hard time getting to the
18 window seat.

19 Q. So can we roll the animation forward, and
20 would you talk over us and tell us what the jury is
21 seeing?

22 A. So this shows the test done in the other
23 direction. So now we're looking to see whether the blue
24 antibody competes with the orange antibody.

25 And because we're looking to see whether it is

1 the orange antibody that's being competed with, we need
2 to be able to measure when the orange antibody is
3 binding TNF.

4 And to do that, we now put the label on the
5 orange antibody. And, remember, the antibodies want to
6 get to their binding sites right here.

7 So we put the animation in play, and now we
8 see that both antibodies can make it to the binding
9 site. The label attached to the orange antibody is
10 attached to the TNF, and we would measure that as a
11 positive signal.

12 We would conclude there was no competition
13 that the blue antibody did not compete with the orange
14 antibody. So here you can see in this animation an
15 example of why the direction that the tests are done can
16 give two different results.

17 Q. Can you give us a real-world example involving
18 TNF-alpha antibodies that demonstrate that there is
19 competition in both directions is important?

20 A. Yes. There was a scientific paper published
21 by Achim Moller and his colleagues in a peer-reviewed
22 journal that demonstrates this.

23 MR. LEE: I'm putting on the screen
24 Defendants' Exhibit 112, which is in evidence, Your
25 Honor.

1 Q. (By Mr. Lee) Is this the publication you
2 referred to?

3 A. Yes, it is.

4 Q. Let me turn your attention to Figures A and B
5 on Page 163.

6 A. Yes.

7 Q. And without going into the details of the
8 figures, have you reviewed the figures?

9 A. Yes, I have.

10 Q. Have you helped us prepare a demonstrative
11 that would make this a little clearer?

12 A. Yes, I have.

13 MR. LEE: Can we bring that up?

14 Q. (By Mr. Lee) So using the demonstrative, which
15 comes from Figure A and Figure B, can you show us what
16 the graphs describe.

17 A. Yes, I will.

18 So we're looking at the -- a test done here to
19 determine if MAK195 and mAB 114 have the ability to
20 compete with each other to bind to TNF-alpha. So two
21 separate tests have to be done.

22 So in the first test, the mAB 114 has the
23 label on it, and we're going to see if MAK195 competes
24 with it. And we measure that competition on the y-axis
25 here as we add in more and more amounts of MAK195, and

1 then we plot the results.

2 And there are other antibodies on this slide,
3 but these are the MAK195 results. And so you can see,
4 when no MAK195 is added, there's a very strong binding
5 signal for the mAB 114. And when there is a lot of
6 MAK195, there is a very strong binding signal for the
7 MAK195. And so MAK195 does not compete with mAB 114.

8 On the right panel, the test is done the other
9 way around. So MAK 195 has the label on it, and we're
10 going to see if mAB 114 competes with it. So here we
11 have no mAB 114, and we have a very strong binding
12 signal for the MAK195.

13 But as we add increasing amounts of mAB 114,
14 the MAK195 signal decreases until it gets very close to
15 zero. So we're comparing this type of result with this
16 type of result, which allows us to conclude that MAK195
17 does not compete with mAB 114, but mAB 114 does compete
18 with MAK195.

19 And then this demonstrates that this concept
20 of that direction matters is not -- as shown in the
21 cartoon animation, is not theoretical, it occurs in the
22 real world, and in this case in a very relevant example,
23 antibodies to TNF-alpha?

24 MR. LEE: Now let's go to Page 163. And
25 there was a portion that, I believe, Dr. Adams was asked

1 about on his redirect.

2 From the left-hand column, could we have
3 that -- could we have the last paragraph of -- and the
4 paragraph preceding it, could we have those taken
5 together and...

6 Q. (By Mr. Lee) Now, I had referred Dr. Adams to
7 a portion at the bottom. Dr. Adams' counsel had
8 referred to a portion at the top. This is referring to
9 Figure 1, correct?

10 A. That's correct.

11 Q. Would you tell us what is being described in
12 terms of the results of both tests in both directions in
13 the Moller paper?

14 A. So what Dr. Moller is describing is what the
15 data in the figures show. And what the data in the
16 figures show, as it says right here, is that mAB 195 did
17 not compete with the other mABs. And that would include
18 mAB 114. So mAB 195 does not compete with mAB 114.
19 And then he says right here, mAB 114 has an influence on
20 mAB 195 binding site but not vice versa.

21 So Dr. Moller has used the word influence;
22 he's not used the word competes with. But when you look
23 at the data, the data clearly show virtually 100 percent
24 competition.

25 Q. Now let's go to the second set of tests, which

1 were between Humira and cA2.

2 A. Yes.

3 Q. You remember His Honor's claim construction
4 requires that the comparison be between Humira and cA2,
5 correct?

6 A. You mean A2.

7 Q. I mean, Humira and A2. I apologize.

8 A. That's correct.

9 Q. All right. Now, when I -- when Dr. Adams was
10 here, as I reviewed with him a portion of the file
11 history and the manner in which the claims changed -- do
12 you recall that?

13 A. I do recall that.

14 Q. And do you recall I reviewed with him the
15 elimination of the phrase cA2 and the limitation to just
16 A2?

17 A. That's correct.

18 Q. And I'm going to set that aside because the
19 file history is before the jury.

20 Let me ask you about this: Is there a
21 difference between cA2 and A2 that would affect the
22 results of a competitive inhibition test?

23 A. There are differences, yes.

24 Q. And what are the differences?

25 A. The A2 antibody is a mouse antibody, and the

1 cA2 antibody is a chimeric antibody. So in the cA2
2 antibody, only 25 percent of the sequence that is
3 present in the A2 antibody is there.

4 Q. And with those differences, could those
5 differences make an effect in competitive inhibition
6 testing?

7 A. I believe they could. They can change the
8 shape of -- the shape and angle of the fab arms, and the
9 antibodies also have different length hinges, which
10 could affect the position of the constant region.
11 So those changes could change the results of the tests.

12 Q. Now, without doing -- let's go back to Humira
13 and A2.

14 Without doing the test in both directions, can
15 you predict what the result would be?

16 A. No.

17 Q. And the same for Humira and cA2. Without
18 doing the test in both directions, could you predict
19 what the tests would be?

20 A. No.

21 Q. The results would be?

22 A. No. You have to do the tests.

23 Q. Have you done the test in both directions?

24 A. No.

25 Q. Has Dr. Adams done the test in both

1 directions?

2 A. No.

3 Q. Okay.

4 MR. LEE: Nothing further, Your Honor.

5 THE COURT: All right.

6 Cross-examination.

7 Counsel, approach just a moment.

8 (Bench conference.)

9 THE COURT: Are you -- I'm trying to
10 prepare a draft of the charge. Is this the only
11 publication you're going to offer testimony on, is
12 Adair?

13 MR. LEE: Yeah. Yeah. I think we gave a
14 list yesterday.

15 THE COURT: Yeah, but now that I'm
16 taking -- I'm going to put down what you've actually
17 testified to.

18 MR. LEE: Yeah.

19 THE COURT: Just be the one publication?

20 LAW CLERK: She gave me three.

21 MR. LEE: Can I just have a moment to
22 check? I mean, we gave you the 1992 before we had the
23 side-bar.

24 THE COURT: Yeah.

25 MR. LEE: So that one is definitely out.

1 I just can't remember...

2 LAW CLERK: The Salfeld patent was the
3 other one.

4 MR. LEE: Well, I think we should address
5 that with Your Honor at some point.

6 THE COURT: We'll leave it in for the --
7 we'll leave in the Salfeld.

8 MR. LEE: Yeah. Take out the '92,
9 though. Try to stay --

10 THE COURT: I understand.

11 (Bench conference concluded.)

12 CROSS-EXAMINATION

13 BY MS. MULLIN:

14 Q. Dr. Marks, nice to see you again.

15 A. It's good to see you again, Ms. Mullin.

16 Q. We actually had the opportunity to take your
17 deposition twice in connection with this case, right?

18 A. That's correct, you did.

19 Q. And I think that somebody has given you copies
20 of each one of those depositions up there in case you
21 need them.

22 A. I've got them.

23 Q. Okay. And there's also two binders up there.
24 Just so you understand what we've given you, one
25 includes exhibits that have been marked as Defendants'

1 Exhibits or DX numbers, and the other one is a binder of
2 Plaintiffs' exhibits that I might talk about with you
3 today, okay?

4 A. Okay.

5 Q. Okay. So I'd like to start with the subject
6 of infringement.

7 A. Okay.

8 Q. And just to be sure we're all on the same
9 page, infringement is measured against the patent
10 claims, right?

11 A. That's correct.

12 Q. This is not a product-to-product comparison;
13 infringement is measured by comparing Humira to the
14 claims in the '775 patent, right?

15 A. Absolutely.

16 Q. Okay.

17 MS. MULLIN: Whoops. Is that right?
18 Okay. Thank you.

19 Q. (By Ms. Mullin) Okay. So let's start and see
20 where we can agree, okay?

21 A. I like that.

22 Q. Humira is an isolated recombinant
23 anti-TNF-alpha antibody, correct?

24 A. Correct.

25 Q. I don't think I can do this sideways.

1 And Humira has a human constant region, correct?

2 A. Correct.

3 Q. And Humira binds to a neutralizing epitope of
4 human TNF-alpha in vivo, correct?

5 A. Correct.

6 Q. And Humira has an affinity of at least 10 -- 1
7 times 10 to the 8th liter per mole measured as an
8 association constant or Ka, as determined by a Scatchard
9 analysis, correct?

10 A. That's correct.

11 Q. And Humira also has a human variable region,
12 right?

13 A. That's correct.

14 Q. And Humira has a human heavy and light chain,
15 correct?

16 A. That's correct.

17 Q. And Humira also has a human IgG1 constant
18 region, correct?

19 A. That's correct.

20 Q. Okay. So we agree that Humira contains every
21 element of the asserted patent claims except for the
22 competition element, right?

23 A. Yes, we do.

24 Q. Okay. And you were here for Dr. Adams'
25 testimony and for Ms. Tam's testimony about the assays

1 that she did, right?

2 A. Yes, I was.

3 Q. And although you don't agree with Dr. Adams on
4 the conclusions that can be reached from this testing,
5 you have not submitted any testing of Humira and A2 for
6 this case, right?

7 A. That's correct.

8 Q. And you relied on an outside laboratory for
9 certain of your conclusions for tests that they had done
10 with A2.

11 A. That's correct.

12 Q. But either they didn't do or they didn't give
13 you the results of testing that they did with Humira and
14 A2, right?

15 A. Excuse me? Oh, that's correct. That's
16 correct. Sorry.

17 Q. Okay.

18 A. I was a bit confused there.

19 Q. That's okay.

20 So I think your counsel used this with you.

21 A. That's correct.

22 Q. Okay. The competition element of the claims
23 is satisfied if Humira competes with A2 for binding to
24 human TNF-alpha, right?

25 A. Correct.

1 Q. And if I understand your position about
2 competition, you agree that Ms. Tam's tests show that A2
3 competes with Humira, right?

4 A. That's correct.

5 Q. You just say that they don't also show that
6 Humira competes with A2 for binding to TNF-alpha, right?

7 A. That's correct.

8 Q. Okay. So you suggested that if she had done
9 the test in a different direction, she could have gotten
10 a different result, right?

11 A. That's correct.

12 Q. So if referring to antibodies X and Y --

13 A. Yes.

14 Q. Okay. Just not -- I'm sorry. I'm writing
15 sideways. That's not very good.

16 And before this litigation started, you
17 yourself had characterized competition assays by just
18 saying that antibody X competes with antibody Y without
19 reference to which antibody was added first, last, or
20 increased in the assay, right?

21 A. You're going to have to show me the context.

22 Q. Sure. Would you like to open up your
23 deposition to Page 179?

24 A. Which deposition?

25 Q. The deposition that I took just about two

1 months ago, in April.

2 A. So what page?

3 Q. 179.

4 A. Yes.

5 Q. Did I ask you during your deposition the
6 following question?

7 QUESTION: Have you ever heard of an
8 assay or have you ever characterized a competition assay
9 by just saying that Antibody A competes with Antibody B
10 without reference to which one is added first, last, or
11 increased?

12 ANSWER: I'm sure there are examples of
13 that.

14 Did I ask you that question, and did you give
15 me that answer at your deposition two months ago, Dr.
16 Marks?

17 A. That was my answer.

18 Q. Okay. And, in fact, you've probably done that
19 in your own publications, right?

20 A. I'm not sure that I have.

21 Q. Okay. Well, perhaps you can read the next two
22 lines of your deposition. If I can refer you to the
23 following two lines.

24 A. Okay.

25 Q. And we'll go back so that we're sure we have

1 the context.

2 On Page 179 of your deposition that I took --
3 I guess it was about two months ago now?

4 A. That sounds about right.

5 Q. A little more than that?

6 When I asked you the question, Have you ever
7 heard of an assay or have you ever characterized a
8 competition assay by just saying that Antibody A
9 competes with Antibody B without reference to which one
10 is added first or last or increased, your answer was,
11 I'm sure there are examples of that.

12 And my next question was: Probably in your
13 own publications.

14 And you answered: There could well be.

15 A. There could be. I just don't know.

16 Q. Okay. Those are the questions that I asked
17 you at your deposition, and those are the answers that
18 you gave me, correct?

19 A. That's correct.

20 Q. Okay. Now, what Ms. Tam did in her
21 competition assays was to coat a plate with TNF.

22 A. That's correct.

23 Q. And then add ample amounts of a mixture of the
24 Humira and A2 antibodies, right?

25 A. That's correct.

1 Q. And since she had a plate coated with TNF and
2 added ample amounts of two antibodies that bind to TNF,
3 they are competing with each other for binding to TNF,
4 right?

5 A. No, they're not.

6 Q. Okay. Dr. Marks, could you please refer to
7 your deposition at Page 182?

8 A. Yes.

9 Q. Beginning at Line 14, the question I asked
10 you: If I have a plate that's coated with TNF, and if I
11 add two antibodies to it, both to bind to TNF -- and you
12 said yes?

13 A. I did.

14 Q. And then I continued with the question: And
15 they're both added in amounts that have more than enough
16 antibody to bind all the TNF there, are they competing
17 for binding to TNF?

18 And your answer was, I think, again, it -- so
19 they can compete with each other for binding to TNF, but
20 they may not -- but they may or may not be able to
21 inhibit binding.

22 A. That's what I said.

23 Q. Okay. And to be clear, you don't criticize or
24 question Ms. Tam's protocol, protocol meaning the
25 procedures she used for the test, right?

1 A. Other than that they were done in the wrong
2 direction, no.

3 Q. And, in fact -- I mean, you don't have any
4 problems with the protocols that she used to generate
5 her data, right?

6 A. Not at all.

7 Q. And you don't question the period of
8 incubation that Ms. Tam used when she let the antibody
9 sit in the well with TNF, right?

10 A. I do not.

11 Q. And you do not question the data that Ms. Tam
12 generated, right?

13 A. I do not.

14 Q. In fact, you don't have any problem with the
15 quality of data generated by Ms. Tam, right?

16 A. The quality is good.

17 Q. And you have not identified any testing that
18 suggests that the testing done by Ms. Tam is somehow
19 incorrect, right?

20 A. No, I have not.

21 Q. So if I understand your testimony, you've said
22 that there could be instances where you would have
23 competition if the test was done in one direction and
24 not another, right?

25 A. (No response.)

1 Q. And I don't have the animation, but this is --

2 A. That's correct.

3 Q. Okay. And I don't have the animation, but
4 this is the -- at least a printout of one piece of the
5 animation that you used to describe this on; is that
6 right?

7 A. That's correct.

8 Q. Now, Abbott's lawyers provided you with a
9 number of publications to consider in connection with
10 this case, right?

11 A. That's correct.

12 Q. And you --

13 A. And I -- and I did searching for public --
14 other additional publications, that's correct.

15 Q. You looked for anything that might be relevant
16 to this case, right?

17 A. I did.

18 Q. Okay. Now, when you were testifying on
19 direct, you said that there were instances that you've
20 identified where competition occurs in one direction but
21 not another, right?

22 A. That's correct.

23 Q. But there was only one paper that you've ever
24 cited that you contend describes the competition assay
25 where you say there was competition in one direction and

1 not another, right?

2 A. That's correct.

3 Q. And that's the Moller paper, right?

4 A. That's correct.

5 Q. And if I followed your testimony on direct --
6 and I'm sorry. I had written something in there.

7 But if I followed what you said on direct,
8 what Moller said is not that mAb 114 competes with
9 MAK195, but that mAb 114 influences MAK195.

10 A. Those are the words that Moller uses, correct.

11 Q. Right. And in other places, Moller talks
12 about antibodies and whether or not they compete with
13 each other, right?

14 A. That's correct.

15 Q. But here, when he's talking about the result
16 of his own testing, the conclusion that he drew was that
17 mAb 114 influences MAK195; he did not say that it
18 competes, right?

19 A. He used the word influence, not -- he did not
20 use the word compete.

21 Q. And if I -- if we try to establish
22 infringement here by saying that Humira influences
23 binding of A2, you would say that we had not proven that
24 Humira competes with A2; isn't that right?

25 A. You would need to show data that Humira

1 competes with A2, and that data would look like what is
2 shown up there for influences, correct.

3 Q. I don't think that was exactly my question, so
4 let me try it again, Dr. Marks.

5 A. Okay.

6 Q. For purposes of establishing infringement, you
7 say that it would not be enough for Centocor to show
8 that the Humira antibody influences binding of A2 to
9 human TNF-alpha. We would have to show something
10 different, that the Humira antibody competes with A2 for
11 binding to TNF-alpha; isn't that right?

12 A. Yes, as defined by the Court in the claim
13 construction, correct.

14 Q. Now, in addition to the testing that was done
15 by Ms. Tam, Dr. Adams also relied on competition tests
16 using cA2 and TNF-alpha, correct?

17 A. That's correct.

18 Q. And one of the things that he talked about was
19 marked as Plaintiffs' Exhibit 137, right?

20 A. I believe so.

21 Q. And these were studies done by an Abbott
22 scientist, Zehra Kaymakcalan, involving cA2 and Humira,
23 right?

24 A. That is correct.

25 Q. And Dr. Kaymakcalan is an Abbott scientist who

1 has a Ph.D. in immunology, right?

2 A. Yes, I believe that's correct.

3 Q. Now, Dr. Kaymakcalan used cA2 in her assays
4 with Humira, but --

5 A. That --

6 Q. I'm sorry. But the part of the antibody that
7 actually binds to TNF is the variable region, the ends
8 of the Y, right?

9 A. That's correct.

10 Q. And in cA2, that binding region is identical
11 to the binding region of A2, right?

12 A. Yes, it is.

13 Q. So although you've testified that an antibody
14 that competes with cA2 for binding to TNF-alpha might
15 not compete with A2, you have never seen an assay where
16 A2 and cA2 do not compete equally well, right?

17 A. That's correct.

18 Q. And you don't have any data suggesting that
19 there is any difference in results when you use A2 or
20 cA2 in testing for competition, right?

21 A. No, I don't.

22 Q. And you cannot point to any evidence that an
23 antibody that competes with A2 will not compete with cA2
24 for binding to human TNF-alpha, right?

25 A. That's correct.

1 Q. And I'm going to say the reverse. But you
2 cannot compete -- or you cannot identify any evidence
3 that shows that there's an antibody that competes with
4 cA2 but does not compete with A2 for binding to human
5 TNF-alpha, right?

6 A. That's correct.

7 Q. In fact --

8 MS. MULLIN: Did it turn off. I'm going
9 to this element.

10 Q. (By Ms. Mullin) You can't even say that there
11 is a 1 percent chance that there is an antibody out
12 there that would compete with cA2 for binding to
13 TNF-alpha but would not compete with A2 for binding to
14 TNF-alpha, right?

15 A. Could you rephrase that to make that question
16 a little simpler? I'm not sure what you're asking.

17 Q. Sure. I'll just say it again.

18 You can't even say that there's a 1 percent
19 chance that there's an antibody out there that would
20 compete with cA2 for binding to TNF-alpha but would not
21 compete with A2 for binding to TNF-alpha; isn't that
22 right?

23 A. I can't say with any percentages. I don't
24 know. You have to do the tests.

25 Q. So my question is, though, you can't even say

1 that there's a 1 percent chance of that, right?

2 A. I don't know what the probability is. I don't
3 know. I don't know.

4 Q. So you couldn't confirm that there's even a 1
5 percent chance that that might happen, right?

6 A. I do not know.

7 Q. Okay. And you understand, for purposes of
8 proving infringement, Centocor has the burden of proving
9 it by a preponderance of the evidence, right?

10 A. That's correct.

11 Q. And what that means, as His Honor explained to
12 us, was that the weight of the evidence must tip ever so
13 slightly in favor of a finding of infringement, and if
14 we've done that, then we have proven infringement,
15 right?

16 A. That's correct.

17 Q. So although you've testified that an antibody
18 that competes with cA2 for binding to TNF-alpha might
19 not compete with A2, you can't even tell us the
20 probability that that might happen, right?

21 A. That is correct.

22 Q. Okay. I'm going to shift things around for a
23 little bit because I'm mindful of the time.

24 Okay. You talked about this demonstrative,
25 which refers to a human anti-mouse antibody response?

1 A. Yes, I did.

2 Q. And you explained to the jury that there can
3 be an immune response to either a mouse antibody or part
4 of a mouse antibody called the HAMA response, right?

5 A. That's correct.

6 Q. And I think you said it can be -- I mean, it
7 can be as extreme as an anaphylactic shock, right?

8 A. That's correct.

9 Q. Well, there's also something known as a HAHA
10 response, isn't there?

11 A. There is.

12 Q. And that is a human anti-human antibody
13 response, right?

14 A. Yes, it is.

15 Q. And that can happen to people who take Humira,
16 right?

17 A. Yes, it can.

18 Q. So if we can take a look, then, at Plaintiffs'
19 Exhibit 66 in your binder, if you'd like to see it, Dr.
20 Marks.

21 A. Are you going to -- are you going to show --
22 do I need --

23 Q. I'll show it on the screen, or you're welcome
24 to refer to what's in your binder.

25 A. Are you going to blow it up so I can see it?

1 Q. Sure.

2 A. I think that's easier than trying to leaf
3 through 20 pounds of --

4 Q. Sure. This is -- this is Humira or
5 adalimumab. This is the prescribing information, right?

6 A. Looks like the package insert.

7 Q. Right --

8 MS. MULLIN: And if we can go to Page 2,
9 under warnings and precautions, if we can blow that up,
10 please.

11 Q. (By Ms. Mullin) Third bullet point down,
12 anaphylaxis.

13 A. Yes, that's what it says.

14 Q. That's anaphylactic shock, right?

15 A. Yes, it is.

16 Q. So the same anaphylactic shock that you
17 explained might happen if you took an antibody that
18 included -- well, a chimeric antibody can also happen
19 taking what you call a fully human antibody, like
20 Humira, right?

21 A. Yes, it can.

22 Q. And if we look at Page 8 under the heading
23 immunogenicity.

24 MS. MULLIN: He'll blow it up for you.
25 Okay. And it can just be the first paragraph. So if

1 you would blow it up big enough so everyone can see.

2 Q. (By Ms. Mullin) Can you read that, Dr. Marks?

3 A. Yes.

4 Q. Okay. What the prescribing information for
5 Humira indicates, that about 5 percent -- and this is
6 the prescribing information for rheumatoid arthritis, so
7 that's why it's referring to rheumatoid arthritis.

8 A. Okay.

9 Q. About 5 percent of the patients receiving
10 Humira developed antibodies to adalimumab.

11 A. That's what it says, yes.

12 Q. That's the HAHA response that we were just
13 talking about, right?

14 A. Yes, it is.

15 Q. Okay. And actually, the very last sentence in
16 that paragraph indicates, the long-term immunogenicity
17 of Humira is not even known, right?

18 A. That's what it says. Yes.

19 Q. So we don't have any data indicating long
20 term, the kind of allergic response that might -- or
21 adverse response that might develop from taking a fully
22 human antibody like Humira, right?

23 A. That's what it says.

24 Q. And I just want to be clear. The reason that
25 people can develop antibodies to Humira or the same

1 reasons they can develop antibodies to a chimeric
2 antibody or a humanized antibody is because Humira is --
3 we're calling it a fully human antibody, but it's still
4 a foreign protein, right?

5 A. It is recognized by some patients as foreign,
6 that is correct.

7 Q. It's not something that's actually made in the
8 body, right?

9 A. It probably would not exist in any individual
10 person, that is correct. Our antibodies are all pretty
11 much unique, yes.

12 Q. And actually, I can't draw a hamster, but what
13 actually happens, what makes Humira a fully human
14 antibody is a hamster, hamster cells, right?

15 A. Humira is produced in hamster cells, that's
16 correct.

17 Q. Okay.

18 A. Chinese hamsters.

19 Q. Chinese hamster ovary cells, right?

20 A. That's correct.

21 Q. To make the record complete.

22 And I know you talked about human antibodies
23 or fully human antibodies as being the Holy Grail of
24 antibodies.

25 A. That's correct.

1 Q. I think you said that a few times, right?

2 A. I -- I'm not counting.

3 Q. Okay. Well, you know that Abbott is currently
4 developing a humanized antibody for an IL-12 antigen,
5 right?

6 A. I'm not sure whether I know that or not, but
7 if you say it's correct, I assume it's correct.

8 Q. So companies can make a choice about which
9 type of antibody to make, right?

10 A. Correct. But currently I'm not aware of
11 companies that are making chimeric antibodies unless
12 they have no other way to make the antibody either human
13 or humanized.

14 Q. So just so I understand, it may be that a
15 company chooses not to go after what you have called the
16 Holy Grail as the antibody of choice for a commercial
17 product, right?

18 A. Humanized antibodies are a perfectly good way
19 to make antibodies, therapeutic antibodies.

20 MS. MULLIN: Your Honor, I'm about to
21 launch into a new subject. I'm happy to go on for five
22 minutes or happy to --

23 THE COURT: Oh, you talked me out of it.
24 It's close enough to lunch for me.

25 All right, Ladies and Gentlemen. We'll

1 take our lunch break. Be back -- ready to come in at
2 1:10, 1:10.

3 Have a nice lunch. Don't discuss the
4 matter. You may leave the courtroom.

5 COURT SECURITY OFFICER: All rise.

6 (Jury out.)

7 THE COURT: You may step down, Doctor.
8 You may step down.

9 THE WITNESS: All right. Thank you.

10 THE COURT: All right. Court will be in
11 recess until 10 after 1:00. I'll see counsel up here.

12 (Bench conference.)

13 THE COURT: Okay. Here's a copy of the
14 rough -- two copies --

15 MS. MULLIN: Okay.

16 THE COURT: -- of a rough draft of the
17 charge. There's not a verdict form on there.

18 LAW CLERK: No, sir. I have a --

19 THE COURT: Well, probably try to have
20 that by the next break.

21 LAW CLERK: I can get it printed out.

22 THE COURT: No. I hadn't look at it yet.
23 So I'll look at that, and I'll give that to you at the
24 first afternoon break. And we'll plan on having an
25 informal charge conference at the close -- after the

1 jury goes home.

2 MR. LEE: Okay. All right.

3 MS. MULLIN: Thank you.

4 THE COURT: Well, unless y'all say we're
5 about to get completely finished. We might wait till in
6 the morning, but I think it would be better if we --

7 MS. ELDERKIN: I doubt that's the case.

8 THE COURT: I don't think -- I think
9 we're going to be using -- we'll be having maybe a
10 conversation about this time tomorrow up here.

11 MR. LEE: That's about right.

12 THE COURT: Okay. Have a nice lunch.

13 MS. ELDERKIN: All right. Thank you,
14 Your Honor.

15 MS. MULLIN: Thank you, Your Honor.

16 (Recess.)

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CERTIFICATION

I HEREBY CERTIFY that the foregoing is a true and correct transcript from the stenographic notes of the proceedings in the above-entitled matter to the best of my ability.

/s/_____
SUSAN SIMMONS, CSR
Official Court Reporter
State of Texas No.: 267
Expiration Date: 12/31/10

Date

/s/_____
JUDITH WERLINGER, CSR
Deputy Official Court Reporter
State of Texas No.: 731
Expiration Date 12/31/10

Date